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PREFACE

The subject of human heredity has grown very rapidly in recent years, especially in relation to medicine. My previous book on this subject, *Heredity in Man*, covered the field fairly well up to 1929 and was an extension of an earlier work, *Heredity and Eugenics* (1923). In the present work the number of chapters has been doubled, the amount of material is perhaps five times as great, and the bulk of the work included has been published since 1929. This is therefore in every sense a new work, greatly enlarged. Although some of the material in the previous book has been incorporated in certain chapters, every chapter contains mainly new material. The approach has been biological rather than more strictly genetical throughout. The first four chapters, which deal with the more genetical and cytological aspects, are entirely new. In Chapters V, VI, IX, XVI and XXIX the material is partly anthropological and Chapter XXX is almost wholly anthropological. The other chapters deal mainly with medical abnormalities of the various organ systems. Eye and hair color, color-blindness, albinism, metabolic errors and allergy each require a chapter. Hemophilia, in which the earlier genetic outlook is greatly changed, requires another. The same is true of other blood diseases and of the blood groups. The latter both involve fundamental advances in racial anthropology as well as in medicine.

The chapter on hereditary syndromes is necessitated by the rapidly increasing number of such conditions which are being recognized in the medical literature. Their history generally follows a uniform pattern. One or a few isolated cases are recognized and published. Other authors follow with similar cases, this phase sometimes extending over many years. At first there is no evidence of heredity, but almost invariably as the disease becomes better known definite evidence of its familial occurrence begins to appear, until finally the evidence of heredity becomes clear and indisputable. In a few cases I have suggested inheritance in connection with syndromes which have not yet reached this final stage. In some syndromes with diverse manifestations, the occurrence of partial expressions poses the question whether a single pleiotropic gene or two or three linked genes are involved.

The chapter on twins and twinning discusses the various theories of twin-origin and statistics on multiple births, and brings together many biological results of the comparative study of twins. The comparisons of one-egg twins are not found in any of the recent books on twins and are of chief value as showing the limits of inheritance. The study of twins has become such a well-recognized method in human genetics that other references to twins are scattered throughout the book. For brevity, the terms *MZ* and *DZ* are used in reference to monozygotic and dizygotic twins respectively.

The chapter on muscular and neuromuscular abnormalities is followed by one on defects of the nervous system, and this in turn by one on mental defects. This sequence makes it clear that no sharp line can be drawn between these three categories. The chapter on normal mental differences might have been greatly extended, but much of the material seemed to be rather outside the province of the present work. Indeed, without much compression and elimination any one of twenty chapters could easily have extended to book size. The vast amount of material claiming a place has made it necessary to reduce discussion to a minimum.

The chapter on cancer endeavors to focus the various theories and the manifold observations and experiments bearing on cancer into one unitary point of view regarding one of the greatest problems of modern biology — that of uncontrolled growth. Constitution and susceptibility in relation to body build will occupy a position of increasing importance in the study of hereditary factors, and the chapter on constitution emphasizes some of the important recent developments in this field.

Throughout the chapters in which various physical and physiological abnormalities are considered, the results of animal genetics, especially with the mammals, are frequently cited when they throw light on the conditions in man. The more advanced genetics of Drosophila often serves to illustrate a fundamental principle, and plant genetics has also been drawn into service occasionally. Other results which continually come into the picture in explaining the nature of an abnormality are those of embryology, tissue culture and biochemistry. Every character has to be studied in its relations to the whole organism. That an inherited biochemical defect can produce serious mental derangement as a constant concomitant is but one of many recent discoveries which bring biochemistry and heredity into intimate relations. In the case of many inherited defects and diseases it has been necessary to enter into the physiology or biochemistry of the condition in order to get some understanding of the ultimate nature of the inherited difference and its relations to the rest of the organism. Far more is known about the biology, physiology, morphology and teratology of man than of any other organism, and this knowledge constantly throws side-lights on the interpretation of his genetics.

In *Heredity in Man* it was, I think, first clearly emphasized that the same inherited condition may be (1) dominant, (2) recessive or (3) sex-linked, in different pedigrees. In the last fifteen years the list of such characters in man has been greatly extended, until this can be regarded as a characteristic feature of human genetics. Exactly what it means is still obscure, but a full explanation may involve an important new principle in genetics. In the interval, the importance of "skipping a generation" — now known as *lack of penetrance* — has also been recognized. In writing this book it has become very clear that dominance and recessiveness are not absolutely distinct categories, but that in different families the genes for a particular condition represent a sliding scale of values; sometimes from strict dominance in one pedigree through partial dominance with more or less frequent skips in another, to complete recessiveness with very incomplete penetrance or expression even in the homozygous condition in still others. Of the various explanations, such as the presence of inhibitors or modifiers, none is at present wholly satisfactory. There is no evidence of a change of dominance gradually taking place in any pedigree. Rather there are genes of different strength for the same abnormality in different families.

A work of this kind will necessarily be used for reference. Many characters in man have been studied from so many different points of view that it is impossible to consider all these aspects in one part of the book. The work on melanin or spina bifida, for example, has been referred to more than once under quite different headings. It is therefore hoped that a good index will make available all the material in this very wide field, and the index should be consulted even when the main treatment of a particular topic has been found. As regards literature, the subject is so vast that only key references and some of the more important ones under each topic can be cited. The papers cited should be sufficient to serve as an introduction to the literature of each topic and it is hoped that few really important recent papers have been missed. But the citations in some fields are naturally more complete than in others. They should be sufficient to serve as a starting point for anyone who wishes to pursue investigations on the inheritance of any particular condition. As in any rapidly developing field, there are limitless opportunities for further research, but the time is now past when anyone can profitably suggest that little or nothing is known about heredity in man.

Finally, it is my pleasant duty to thank those who have contributed in various ways to the production of this book. Writing under war conditions and away from my own library has been a source of difficulties; but this has been to a large extent overcome through the facilities offered by the excellent and varied library of the Marine Biological Laboratory. Indeed, I know of no single library which could more adequately and conveniently fulfill the needs associated with the writing of a book of this kind from a biological point of view, although it of course lacks some of the more specialized medical and anthropological journals. During the four years in which this book has been in preparation, I have received generous services not only from the Library staff of the M. B. L. but also from those of the Boston Medical Library, and the Harvard Medical Library, to which occasional visits have been made; I have also been able to make some use of the Howe Ophthalmological Library and, through Professor E. A. Hooton, of the Harvard Anthropological Library. I am greatly indebted to the American Philosophical Society for a grant in connection with secretarial work entailed in the writing of this book.

I have also benefited from a critical reading of Chapter XV by Dr. Eric Ponder, Chapter XX by Dr. L. H. Snyder and Chapter XXVI by Dr. C. C. Little, but the views expressed are of course my own responsibility. I am further indebted to Dr. L. C. Dunn, Dr. Madge Macklin and others for several references, and to Dr. Snyder for aid with references.

The selection of illustrations has been a difficulty, because it is impossible to illustrate more than a tithe of the conditions considered. Figure 168 is from an original photograph contributed by Dr. R. M. Stecher of Cleveland, Fig. 181 was similarly provided by Dr. W. W. Graves of St. Louis, Fig. 274 by Dr. E. Witschi and Fig. 65 by Dr. D. G. Cogan of the Massachusetts Eye and Ear Infirmary. The photomicrograph in Fig. 230 is from a preparation made in the laboratory of Dr. C. H. Smith, New York University, and Fig. 256 is from Dr. S. Levine, Dept. of Pediatrics, New York Hospital. The original source of publication of all the others is given under the figure, the author's name serving as a guide to the full citation of the journal in the Literature list. Sixty-five figures and pedigrees are reproduced here from *Heredity in Man*, the publishers, Messrs. Constable, having kindly sent me the blocks for this purpose. I also have to thank the Duke University Press for the loan of the blocks for Figs. 117 and 307 from Snyder's *Medical Genetics*. The rest have been collected from many journals.

The pedigrees have frequently required complete reconstruction, often with change to the standard symbols, which it is hoped that medical journals will adopt more fully. One finds from experience that they are greatly preferable to the old symbols, ♂ ♀. The latter are a frequent source of error and difficulty in pedigrees, especially when printed rather small or on paper which is not quite smooth. Medical men lead busy lives, but the extra time required in transcribing their pedigrees into the standard symbols, making sure that the pedigrees correspond with the statements in the text and in giving the sex and condition of every member of the pedigree, is no more than sufficient to meet the conditions of more accurate and detailed statement which are necessary in the stage of statistical enquiry which human genetics has now reached. It is impossible to use some published pedigrees, except for limited purposes, because of one or more of the defects just mentioned. If medical men and others will give in their pedigrees the additional accuracy and detail now required, they will greatly aid in the further rapid advance of human genetics.

For clerical assistance in the preparation of the manuscript I am especially indebted to Mrs. Kent T. Smith, Mrs. L. G. Barth, Mrs. K. G. Hall and Miss V. C. Peckham.

In the interval since the above was written, delays have arisen partly due to the war. I have had the benefit of a critical reading of Chapter II by Dr. K. Brehme, Chapter XXI by Dr. E. G. Conklin, Chapter XXIII by Dr. C. L. Huskins, and Chapter XXX by Dr. E. A. Hooton. I am also greatly indebted to Professor Hooton for his interest and aid in connection with the publication of this work. Professor George Sarton has contributed the reference to Hunain and I have received courtesies and help from the Harvard Library and that of the New York Academy of Medicine.

Some of the material here assembled was used in a series of eight lectures on human heredity at the Lowell Institute, Boston, in October and November, 1944.

Permission has been obtained for publication of the following figures:

Fig.	52	Usher in *Ann. of Eugen.* 1:128, pl. 4.
	53	Cockayne in *Proc. Roy. Soc. Med.* 24:847.
	87	Potter in *J. Hered.* 28:255, Fig. 10.
	92	Edmonds & Keeler in *J. Hered.* 31:507, Fig. 2.
	94	Whitney in *J. Hered.* 30:323, Fig. 1.
	103	Nussey in *Lancet,* 235:947.
	107	McGuire & Zeek in *J. Am. Med. Assn.,* 98:871, Figs. 2, 3.
	111	Ellis in *Proc. Roy. Soc. Med.* 29:748.
	116	Ingram & Oldfield in *Brit. Med. J.* i:960 (1937), Fig. 6.
	127	Clemente in *J. Hered.* 19:528, Fig. 5.
	128	J. Smith in *Proc. Roy. Soc. Med.* 24:323, Fig. 1.
	140	Thomsen in *Hereditas,* 10:265, Fig. 1.

Fig. 142	Koenner in *J. Hered.* 25:329, Fig. 16.
144	Hefner in *J. Hered.* 32:37, Fig. 14.
146	Penhallow in *J. Am. Med. Assn.* 91:564, Fig. 4.
152 153	Manoiloff in *Am. J. Phys. Anthrop.* 15:506–7, Figs. 1a, 2a.
154	Cummins in *Am. J. Anat.* 51:412, pl. 1, Fig. 10.
157	Snyder in *J. Hered.* 20:73, Fig. 6.
167	Tallerman in *Proc. Roy. Soc. Med.* 25:1731.
169 170	MacArthur & McCullough in *Human Biol.* 4:181–4, Figs. 1–5.
173	Wilcox in *Am. J. Roentgenol.* 27:581, Fig. 1.
175	Smith in *J. Am. Med. Assn.* 102:593, Fig. 1.
176	Goldsmith in *J. Hered.* 13:69, Fig. 11.
182	Snyder & Curtis in *J. Hered.* 25:445, Fig. 10.
183	Caldwell & Moloy in *Proc. Roy. Soc. Med.* 32:5, Fig. 2.
184	Greulich & Thoms in *J. Am. Med. Assn.* 112:492, Fig. 10.
190	H. Moore et al. in *Quart. J. Med.* 29:516, pl. 16, Fig. 4.
194	Ellis & Payne in *Quart. J. Med.* 29:31, Fig. 1.
195	Bloem, Groen & Postma in *Quart. J. Med.* 29:517, Fig. 1.
198	Muller in *Arch. Int. Med.* 64:678, Fig. 2.
199	Watson & Ritchie in *Quart. J. Med.* 18:239, pl. 8, Fig. 2.
207	Eugster in *Arch. J. Klaus-Stift.* 13:476, Fig. 55b.
229	Lawrence in *Am. J. Med. Sci.* 181:240, Fig. 1.
251	Ornsteen in *Am. J. Med. Sci.* 183:262, Fig. 4.
254	Miller in *Am. J. Phys. Anthrop.* 14:79, pl. 1, Figs. 1, 2.
258	Mörch in *J. Hered.* 31:439, Fig. 5.
259	Kelley in *J. Hered.* 20:352, Fig. 1.
260	Burke in *Proc. Roy. Soc. Med.* 24:418, Fig. 3.
268	Graham-Campbell in *Brit. Med. J.* i:471 (1936), Fig. 1.
269	Christie in *Brit. Med. J.* i:780 (1938), Fig. 1.
274	Witschi & Mengert in *J. Clin. Endocrinol.* 2:280, Fig. 1.
279	Black in *J. Hered.* 31:16, Fig. 3.
286	Macklin & Bowman in *J. Am. Med. Assn.* 86:615, Fig. 3.
304	Davidenkoff in *Arch. of Neur. & Psych.* 20:1247, Fig. 10.
315	Draper & Dupertuis in *J. Clin. Investig.* 18:91, Fig. 2.
321	Whitney, *Family Treasures*, p. 135, Fig. 123.
324	Edwards & Duntley in *Am. J. Anat.* 65:5, Fig. 2.

In each legend, under the numerous pedigrees and illustrations, I have credited the original author in every case, and the full journal reference will be found in the bibliography at the end of each chapter. The references to the *Journal of Heredity* have been added at the special request of the editor.

The genetic complications of the **Rh** blood factor have been developing so rapidly while this book was passing through the press that a straightforward account of the latest phases was almost impossible, but references are given to most of the papers. A definitive understanding of the numerous Rh and Hr alleles has probably now been reached.

It would be impossible to assume that a work of this size and scope is free from error and I should be glad if readers would point out to me any misstatements they may find. It is hoped that this work will be of service both to medical men and physical anthropologists in synthesizing certain aspects common to their two fields.

I am indebted to Professor C. Stern, of the University of Rochester, for many helpful comments and criticisms in his reading of the galley proofs, but the views expressed are of course my own.

Finally, I should like to express my thanks to the publishers for the great care and skill they have exercised in every technical phase of the production of this work.

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GENERAL WORKS BEARING ON HEREDITY IN MAN

Berry, R. J. A. & Gordon, R. G. 1931. *The Mental Defective.* London. Pp. 225.

Blacker, C. P. (Editor). 1934. *The Chances of Morbid Inheritance.* London and Baltimore. Pp. 449.

Brain, W. R. 1933. *Diseases of the Nervous System.* London.

Cockayne, E. A. 1933. *Inherited Abnormalities of the Skin and Its Appendages.* Oxford Press. Pp. 394.

Crew, F. A. E. 1927. *Organic Inheritance in Man.* London. Pp. 214.

Cummins, H. & Midlo, C. 1943. *Finger Prints, Palms and Soles* Philadelphia. Pp. 309.

Draper, G. 1924. *Human Constitution.* Saunders. Philadelphia.

Garrod, A. E. 1931. *The Inborn Factors in Disease.* 2nd Ed. Oxford Press. Pp. 160.

Gates, R. R. 1929. *Heredity in Man.* Constable. London and New York. Pp. 385.

Hogben, L. 1931. *Genetic Principles in Medicine and Social Science.* London. Pp. 230.

Hogben, L. 1933. *Nature and Nurture.* London. Pp. 144.

Hooton, E. A. 1938. *Apes, Men and Morons.* Putnam. Pp. 307.

Lidbetter, E. J. 1933. *Heredity and the Social Problem Group.* 2 Vols. London.

Macklin, M. T. 1935. The role of heredity in disease. *Medicine* 14:1-75.

Mann, Ida. 1937. *Developmental Abnormalities of the Eye.* Cambridge. Pp. 444.

Midlo, C. and Cummins, H. 1942. *Palmar and Plantar Dermatoglyphics in Primates.* Wistar Inst. Pp. 198.

Mohr, O. 1934. *Heredity and Human Disease.* New York. Pp. 253.

Myerson, A. 1925. *Inheritance of Mental Diseases.* Baltimore.

Penrose, L. S. 1933. *Mental Defect.* London. Pp. 183.

Penrose, L. S. 1934. *The Influence of Heredity on Disease.* Lewis. London.

Roberts, J. A. Fraser. 1940. *An Introduction to Medical Genetics.* Oxford Press. Pp. 265.

Rosanoff, A. G. 1938. *Manual of Psychiatry and Mental Hygiene.* 7th Ed. New York. Pp. 1091.

Rousseau, Jacques. 1945. *L'Hérédité et L'Homme.* Quebec. Pp. 250.

Rüdin, E. *Studien über Vererbung und Entstehung geistiger Störungen.* Berlin.

Scheinfeld, A. 1939. *You and Heredity.* New York.

Schwesinger, Gladys C. 1933. Heredity and environment. *Studies in the Genesis of Psychological Characteristics.* New York. Pp. 484.

Snyder, L. H. 1940. *The Principles of Heredity.* 2nd Ed. New York. Pp. 452.

Snyder, L. H. 1941. *Medical Genetics.* Duke University Press. Pp. 130.

Spearman, C. 1927. *The Abilities of Man.* London.

Thomson, G. H. 1939. *The Factorial Analysis of Human Ability.* University of London Press.

Verschuer, O. v. 1937. *Erbpathologie.* 2nd Ed. Dresden. Pp. 244.

Wildenskov, H. C. 1934. *Investigations into the Causes of Mental Deficiency.* Oxford Press. Pp. 106.

HUMAN GENETICS

Chapter I

INTRODUCTION

A SURVEY of modern developments in human genetics is a very large undertaking. To be complete it must cover practically the whole literature, both of medicine and of physical anthropology. A fully documented work of this kind would require a score of large volumes. In order to bring this material within the covers of two volumes, it has been necessary to curtail descriptions and generally to refer only to the more important or significant contributions. Chapter XXX is devoted almost entirely to anthropological characters and their inheritance. But in many other chapters, such as those on eye and hair color, stature, blood groups and constitution, anthropological materials have been introduced in comparison with observations more purely medical in nature. It is impossible and undesirable to draw any hard and fast line between the two fields, because some diseases, such as thalassemia, favism and sickle cell anaemia, are more or less confined to certain races. and many other pathological conditions are more frequent in some races than others. A number of differences in racial susceptibility are also known.

This work is intended as a source book for all those concerned with medicine or anthropology in its genetic aspects. It has become clear that every medical condition has its hereditary as well as its physiological aspects, sometimes one and sometimes the other being of paramount importance. But the doctor who neglects heredity loses sight of a great deal of the material which would be invaluable in interpreting his patient's disease in its family history. Since families differ even in their reaction to common infections and diseases, an analysis of the family background of heredity may be of service even in the most unexpected cases. This is also where the general practitioner, with a personal knowledge of his patient's family, has an advantage over the specialist to whom the patient may be simply a case.

This book follows the general plan of my *Heredity in Man* (1929); but the order of the chapters has been changed, their number is increased from sixteen to thirty-one, and the chapter on racial crossing is omitted because the subject requires treatment in a separate book. The bulk of the material in each chapter is new, but in certain chapters portions have been incorporated from the older work. The aim is to make available present knowledge on the inheritance of all kinds of human differences, normal and abnormal, and the present status of research as regards each condition referred to. In the more important cases a short account of the development of knowledge is given, from the discovery of a particular disease to the present understanding of its inheritance. Where different views are held regarding the manner of inheritance of any condition, they are all given as a basis for further analysis unless it is clearly possible to choose between them. Notwithstanding the great advances made in knowledge of human heredity in the last fifteen years, there are still many obscure points, in fact the text will be found to bristle with them. Subjects on which further research is desirable have frequently been indicated.

Human genetics is in one sense an applied science — the results of experiments with animals and plants are applied to the interpretation of human pedigrees and statistics. This has sometimes resulted in a slight tendency to the development of fads, as in the case of modifying factors and multiple factors as applied to human genetic conditions. The advances in the subject have nevertheless been substantial in many directions, and in the aggregate a great body of increasingly accurate knowledge of human genetics has accumulated. The study of linkage, which began with sex-linked characters, has now extended to the other chromosomes and promises to include some of the most important future advances. The development of methods for culturing leukocytes from the blood of living individuals and thus studying their chromosomes promises also important future developments in determining aberrant cytological conditions in individuals, as well as racial differences in the size and gene content of certain chromosomes.

The approach in this book has been biological rather than purely genetical, and when embryological or experimental work of any kind with animals throws light on some condition in man it has generally been quoted. Genetical work, especially with mammals, has also been referred to whenever the conditions or the problems were similar, but there has been no attempt to make these references complete. Green (1938) published a useful comparative summary of morphological mutations in rodents, many of which are comparable with those in man, and Grüneberg (1943) has recently published a comprehensive summary of mouse genetics. The absence of any certain case of a sex-linked abnormality in rodents contrasts strongly with the condition in man. This is probably because in these animals there is crossing-over between the sex chromosomes, a view which is supported by Koller's (1936) observation that in the gray squirrel the X and Y show very little difference in size, their terminal pairing segments being small and the centromere located at the junction of the pairing and differential segments.

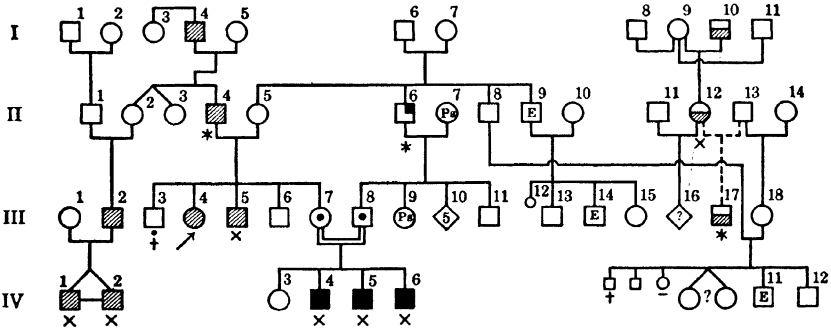
Whenever special problems, such as the formation of melanin or the development of the vertebrate eye or the sex organs, have arisen, they are dealt with *ad hoc* and not as part of any generalized scheme for the book. In the same way, the inheritance of situs inversus viscerum has been dealt with in the chapter on twins, in connection with problems of mirror-imaging. A completely scientific classification of the innumerable characters — normal and abnormal — now known in man is impossible, because of the many cross-relationships and complications. For this reason, essentially the same condition may even occasionally be treated under two different heads; but it is hoped that a full index will make it easy to get all the information available on any particular topic.

An increasing number of medical men who have become interested in heredity have made important contributions to the subject. As genetical knowledge and understanding spreads, their number will no doubt be augmented more rapidly. In the making of pedigrees there has been great improvement, but some of them are still deplorably put together and published. As regards symbols, medical journals and writers still frequently adhere to the ancient symbols, ♂ ♀, for male and female, but one finds from experience that these are more difficult to read and more subject to error, especially when printed rather small, than the symbols used here. Figure 1 shows the various symbols for pedigree charts which were adopted internationally by the Federation of Eugenic Organizations for research in human heredity. After having much experience with both, there is no doubt that the newer symbols are greatly to be preferred for ease and accuracy in reading charts, and it is hoped that the medical profession will adopt them to an increasing extent. These symbols are for the most part self-explanatory and are all that is required for most occasions. Others can be added for special purposes, such as indicating whether the left or the right side of the body is affected. For most purposes not all of them are required.

It is important that all who are concerned with human heredity should learn to "read" pedigrees, drawing from them all the information they contain regarding the manner of inheritance of the gene or genes concerned. A pedigree is seldom as clear and conclusive as a diagram, unless it is large or the gene shows 100 per cent penetrance. Especially in short pedigrees alternative interpretations may be possible, and the real method or methods of inheritance may emerge only after comparing several pedigrees of the same condition.

Medical literature is overburdened with names for diseases. Five or six names for one condition are really too many. In such cases a couple of the names in most common use or which appear most appropriate have been adopted. It is to be hoped that some internationally agreed method of curtailing and controlling disease nomenclature can be adopted in the future. One scientific name for each disease or abnormality, and one name based on the discoverer, should be enough.

In this book, a list of references is given at the end of each chapter, and a list of general works on human heredity after the list of tables in the roman numbered introductory pages. When the same paper is referred to in different chapters, the reference is usually given only once, but not necessarily the first time. The literature on many topics



A. STANDARD FOR ALL PEDIGREE-CHARTS:

□ = Male
○ = Female
◇ = Sex unknown
◇ = Sex unknown, number unknown
◇ = 5 children, sex unknown
× = Tested by investigator himself
* = Tested by other competent person

= Non-identical twins
= Identical twins
= Twins uncertain if identical or not

▣ = Carrier
□ = Abortive male
□ = Premature male
□ = Deadborn male
† = Died in infancy
↗ = Points to propositus (probandus)

□○ = Parents
□○□ = Children
□○ = Parents not married
□ = Illegitimate child
□○ = Consanguinous marriage

Roman figures to the left indicate generations

Arabic figures locate individuals (thus III.7 = the woman in the generation of the propositus who married her cousin. I.9 = the woman in the second ascending generation who married 3 times, respectively with I. 8, 10, 11)

B. ESPECIALLY DEVISED OR SELECTED FOR THIS PARTICULAR PEDIGREE-CHART:

▨ ● = Polydactyly ■ ● = Deafmuteness ◳ = Deafness Ps = Psychopathic E = Epileptic
⊟ ⊖ = Strongly curled hair Other symbols may be added as needed.

Fig. 1. Explanation of international pedigree symbols.

is so vast that only a selection of references is usually given, including key references from which the full literature will be obtainable. Owing to war conditions it has not been possible to consult certain papers which would otherwise have been available. These are marked in the bibliographies with a *.

The medical journals abound with accounts of single cases or a few unrelated ones. Anyone making a survey of these cases for any particular disease must needs use the medical reference works, which are well indexed. Single cases were formerly supposed to be non-inherited, but a fuller understanding of human genetics indicates that many are dominant mutations and others are the outcrops of a recessive gene. Evidence on the last point can be obtained from records of the frequency of cousin marriage among the parents, which is therefore an important datum.

Much of the abundant work on twins and the inheritance of twinning is brought together in Chap. XXI, but frequent reference to inheritance in twins is scattered throughout the other chapters. For the sake of brevity, MZ has been adopted for monozygotic (identical) and DZ for dizygotic (fraternal) twins. When the latter are of the same sex the symbol DZS may be used, and DZU when they are of unlike sex.

An understanding of the manifold action of heredity is so important for the future of mankind that it is to be hoped this book will aid in spreading a knowledge of the subject, not only among medical men, anthropologists and geneticists, but among the general public. The human races agree with wild species in that defective mutations appear in them from time to time and many are carried in the germplasm. In wild species, however, natural selection generally prevents the multiplication of defective types. The least that man can do for his own species is to prevent these defectives from propagating their kind — a thing which rarely occurs in nature.

LITERATURE

Gates, R. R. 1929. *Heredity in Man.* London: Constable. Pp. 385. Figs. 87.

Green, C. V. 1938. Homologous and analogous morphological mutations in rodents. *Biol. Reviews* 13:293–306.

Grüneberg, H. 1943. *Genetics of the Mouse.* Cambridge University Press & Macmillan, New York. Pp. 412. Figs. 43.

Koller, P. C. 1936. Chromosome behaviour in the male grey squirrel (*Sciurus carolinensis leucotus*). *Proc. Roy. Soc. Edinb.* 56:196–209. Figs. 12.

Chapter II

GENERAL PRINCIPLES OF HEREDITY IN MAN

MANY peculiarities of human heredity are considered throughout this work in connection with particular abnormalities or conditions in which they occur, but some of the more general principles may first be considered here.

It is now recognized that nearly all heredity is Mendelian, in the sense that genic differences are transmitted from generation to generation. Genetic research shows that some of the genic differences which arise in the chromosomes are due to physical changes — deletions — the actual loss of a minute fragment of a chromosome. This loss behaves in heredity as a simple Mendelian difference, present in every cell and producing an external (phenotypic)[1] effect in one or more parts of the body. On the other hand, certain dominant mutations in Drosophila, such as bar eye, are known to result from duplication of a few segments of a chromosome. Other genes appear to be of the nature of a chemical change at one locus of a chromosome.[2] Thus we recognize that mutations which arise in chromosomes are of fundamentally different kinds (Gates, 1938), but each is inherited as a Mendelian unit. The human germplasm contains innumerable "genes," some normal and some pathological, presumably resulting from such changes in the chromosomes. Some of these genes represent racial differences which have arisen through isolation in the evolution of mankind. Some represent rare pathological conditions and some, such as the genes for blue eyes or fair hair, are widespread in certain races.

The principles of Mendelian heredity are thus found to be applicable everywhere to man. In the absence of experimentation, however, statistics and twin studies are valuable adjuncts in the analysis of the inheritance of any particular condition. Since Mendelian principles are now more widely known and are set forth in numerous textbooks, a short account of their application to man will suffice.

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[1] The term *phenotype* refers to the external appearance of an organism — the expression of its *genotype* or inherited qualities as a result of interaction with the environment in development.

[2] I first pointed out many years ago (Gates, 1915) that "genes" are essentially *differences*, arising in a chromosome.

In the different races of man, as in related species of animals and plants, mutations have happened, not infrequently as parallel mutations, or similar germinal changes in different lines of descent (see Gates, 1920). Many cases of probable mutation in man are cited in the present work. The same mutation probably always occurs at the same chromosome locus. But the chromosomes themselves undergo rearrangements of their genic material through crossing-over between different chromosomes and in other ways such as inversions of a portion of a chromosome and translocations from one chromosome to another. For recent discussions of these problems, see Dobzhansky (1941), Waddington (1939) and Sturtevant and Beadle (1939). For example, *Drosophila melanogaster* and *D. pseudoöbscura* are known to have fifty-four parallel mutations (Sturtevant and Tan, 1937); but the arrangement of these genes is quite different in the chromosomes of the two species, owing to interchanges and reversals in segments of chromosomes which have since occurred independently in different populations. Evidence has begun to appear that similar rearrangements have occurred in some of the races of man during their long period of isolation.

In nearly all organisms the chromosomes are in homologous pairs and in every human individual one member of each pair has been derived from the father and one from the mother. These chromosomes are generally homologous throughout their length, so that they correspond gene for gene. But human beings are hybrid for a great many characters, so that homologous genes occupying corresponding loci in the two chromosomes of a pair frequently differ from each other. They will then be inherited as a pair of Mendelian characters and are known as *alleles*,[3] one of which represents a mutational change from the condition of the other. Any one organism can usually carry only two allelic forms for each gene. But some genes can undergo a number of different mutational changes. There is some reason to hold, for instance, that the five types of hair form, straight, wavy, curly, kinky and peppercorn, are all different mutations in the same locus of a chromosome. If that is so, they are *multiple alleles*, but only two of them can be present in any one individual. We shall encounter many probable cases of multiple alleles in human genetics. Any one of them can replace any other of the series in heredity.

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[3] Alleles which are indistinguishable except by special breeding tests have been called *iso-alleles* (Stern and Schaeffer, 1943). They are probably of wide occurrence in wild organisms.

Three general types of Mendelian heredity are commonly recognized, in which the gene may be dominant, recessive or sex-linked. In man, unlike many other organisms, the majority of the mutations which occur are dominant,[4] in the sense that one dose of the gene produces a phenotypic (visible) effect. But in most of these cases only the heterozygous (one dose) condition is known, because affected persons almost invariably marry normals. In some instances, however, the homozygous (two dose) condition is known to be more extreme, and it may even be lethal in effect. This of course means that the single gene is not completely dominant, and this condition applies widely in mankind. It also applies to some so-called dominant characters in other organisms.

As a typical example of a dominant character in man, we may take a pedigree of optic atrophy in a Chinese family (Fig. 2, see also p. 215).

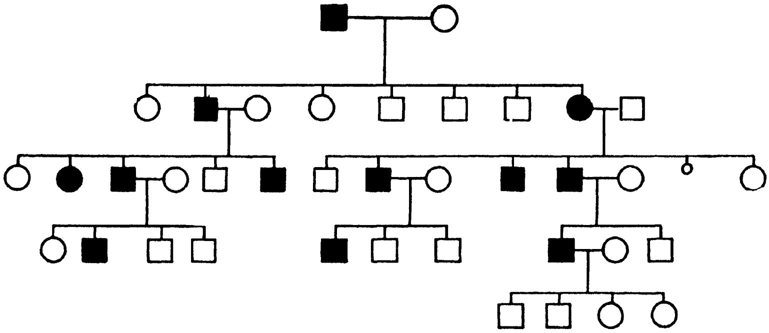

Fig. 2. Yo's Chinese pedigree of optic nerve atrophy. (After Komai)

It will be noted that every affected person had an affected parent and that roughly half the members of each family (sibship) are affected and half normal. In this pedigree there is a considerable excess of affected males, which might be significant, and the various sibships number 11 affected : 19 normal where equality would be expected. By simple statistical methods, the probability that this is a significant departure from equality can be determined. Single pedigrees, unless quite extensive, are often open to doubt on points of this kind and the more extensive pedigrees are too bulky to reproduce here.

It will be understood that half the germ cells of an affected man or woman will carry the defect and half will not, since the gene for this defect is carried in one member only of a particular pair of chromosomes. These separate in the maturation divisions so that every germ cell gets the affected or the normal member of this pair. In a strictly dominant pedigree, in the sense in which the term is used here, about half the children of an affected parent will be affected and half normal, the condition thus appearing in every generation, and in considerable numbers if the families are large.

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[4] The general slackness of natural selection in civilized man will account for this frequency of dominant abnormalities, since abnormal individuals are allowed to reproduce. Sex-linked recessive genes are allowed to multiply in the same way. They are seldom found in nature.

To estimate whether the divergence of normal and affected from equality is significant, the formula $\frac{(p - q - 1)^2}{p + q} = d$ may be used, where p and q are the total numbers of normal and affected respectively in the sibships. In the above dominant pedigree of optic atrophy there are 11 affected : 19 unaffected. This gives the value $d = 1.6$. If d is less than 4, the difference is not significant. If the ratio were 11 : 24, d would be 4.1 and significant.

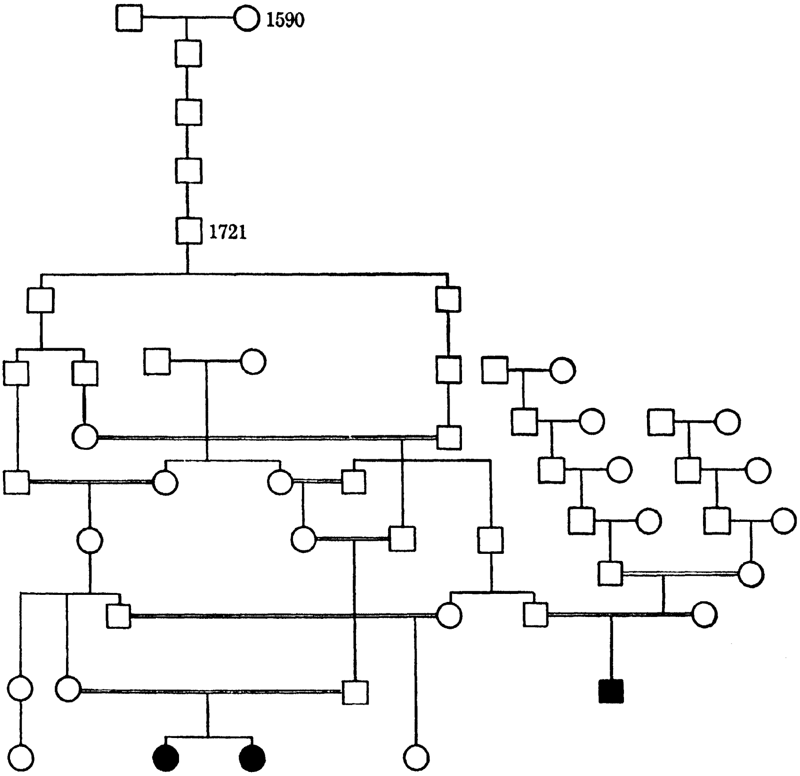

Fig. 3. Pedigree of recessive epidermolysis bullosa. (After Jenny)

By contrast, a recessive pedigree presents a very different appearance. Figure 3 shows a pedigree of recessive epidermolysis bullosa (see also p. 298). The condition was absent from the ancestors in this family for ten generations, then suddenly appeared with three cases in two families descended from ancestors in which there had been eight consanguineous marriages (indicated by double lines). Many of these ancestors were heterozygous for this gene producing blisters of the skin; but only when two such persons marry is there a chance of the disease appearing, through the production of children who are homozygous for the gene, i.e., have received it from both their parents. This chance is one in four when both parents are heterozygous, so that in large unrestricted families only one-fourth of the children will be affected, whereas in a dominant pedigree the number of affected siblings (brothers and sisters) is one-half. The three sibs in these two families were all affected, probably because the parents restricted their families after the disease appeared, perhaps realizing its inheritance. A recessive gene may thus be transmitted through many generations with no visible effect, and then cousin marriages in a family which is carrying it may suddenly bring it to the surface. The rarer the gene the more likely it is to appear only in the children of consanguineous marriages. If an individual is heterozygous for a recessive gene, the probability that his first cousin also possesses it is one-eighth. A common recessive gene, such as that for blue eyes, of course appears frequently in the children of two brown-eyed parents who are unrelated, because this gene is very common in most Caucasian populations. In determining the method of inheritance of a particular gene, it is therefore an advantage to know, especially in the case of rare genes, whether the parents were related. Those compiling pedigrees should pay particular attention to this point. In general, a recessive pedigree of any abnormality will contain far fewer affected individuals than a dominant pedigree.

In such conditions as retinitis pigmentosa there may be a number of independent recessive genes. Whether they are really different can only be determined when members of two different pedigrees intermarry. If the genes are different all the children will be normal, but if they are the same all the children will be affected like their parents.

The third common type of heredity in man is sex-linked recessive. This depends upon the fact (see Chap. III) that man, like many mammals, insects and other animals, has a pair of sex chromosomes which act as a switch in throwing the development of the individual into the male or the female line. A man has a large X- and a small Y-chromosome, while a woman has two equal X-chromosomes in her cells. These, especially the X, have many genes besides those which control sex-determination. Half the sperm contain an X and half a Y. All the eggs after maturation contain an X. If a Y-sperm fertilizes an egg it determines a male with an XY pair, but if an X-sperm enters the egg, a female is produced with a pair of X-chromosomes.

Color-blindness is inherited as a sex-linked recessive character, i.e., it is transmitted by an affected man to all his daughters, because it is in his X-chromosome. These daughters will be normal, although heterozygous, because the gene for color-blindness is recessive and is dominated by the corresponding normal gene in their other X chromosome. But half their sons by a normal man will receive an affected X from their mother. There is no corresponding gene in the Y, so those sons are color blind. This unbalanced condition of a gene, in which it has no mate, is called *hemizygous*. Wilson's (1911) explanation of the basis of sex-linked inheritance was one of the most significant discoveries in the history of genetics. Sex-linked recessive inheritance is sometimes called *gynephoric* (Waardenburg, 1932) since normal women are carriers. This term is particularly applicable to some pedigrees of hemophilia in which the affected males rarely or never attain an age for reproduction. Another criterion of sex-linked inheritance, distinguishing it from dominance, is that the inheritance is never directly from father to son, because the X-chromosome passes always to the

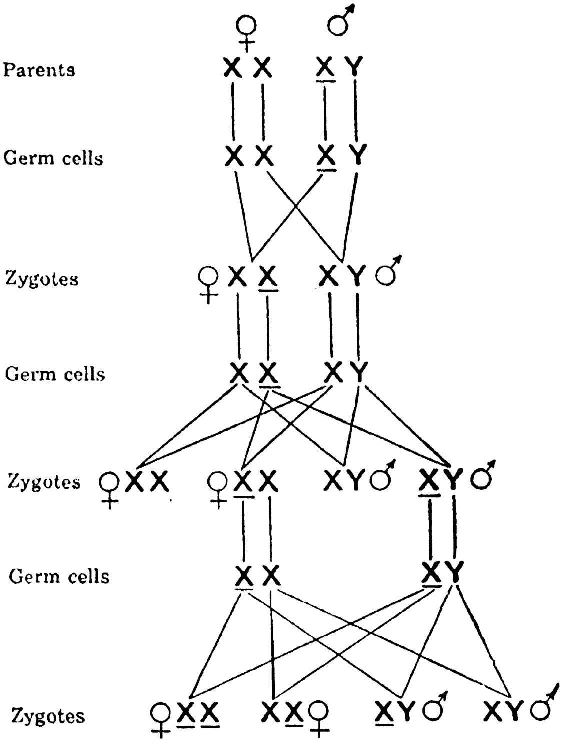

Fig. 4. Diagram to illustrate the inheritance of sex-linked characters through the X-chromosome. (Modified after Wilson)

daughters, while the son gets his X from his mother. Still another is that, if there is intermarriage, affected (homozygous) females may occur, but as recessiveness is frequently incomplete, heterozygous females are sometimes also affected.

From Fig. 4 it will be seen why this law of sex-linked inheritance holds. The underlined X is carrying any recessive sex-linked character such as color-blindness or hemophilia. This X is transmitted from the male of one generation to the female of the next, where the gene is recessive. In line five of the diagram she transmits it to half her sons (who are color blind because in them the gene has no mate) and half her daughters, who are carriers but normal, like herself. The last two lines of this diagram illustrate the rarer condition in which a carrier for color-blindness marries a man who is color blind. It will be seen that half the daughters in this case will be color blind because they are homozygous for the condition, and the other half will be normal but carriers. Half the sons will be normal and half color blind. The ratio of these four types is thus 1 ♂ : 1 ♂ : 1 ♀ : 1 ♀. The sex chromosomes thus, as Wilson (1911) first pointed out, offer a complete explanation of this complicated type of heredity, for which there was previously no explanation at all. Usually the condition will appear only in the males of alternate generations, but daughters homozygous for color-blindness will transmit it to all their sons, and all their daughters will be carriers.

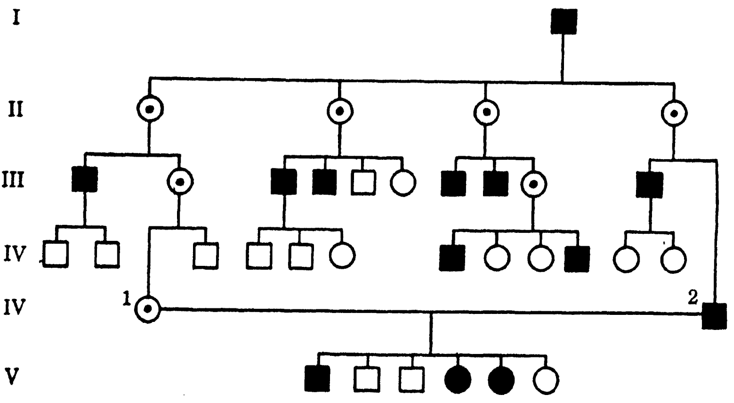

Fig. 5. Pedigree of recessive sex-linked ichthyosis vulgaris.

Figure 5 shows a typical recessive sex-linked pedigree of ichthyosis vulgaris. The four daughters of the man in generation I were carriers because they received his (affected) X-chromosome. In generations III and IV there were nine affected to six normal sons, where equality is expected. The mother of generation V was a carrier and the father was affected as well, so the children were 1 ♂ : 2 ♂ : 2 ♀ : 1 ♀ where a ratio of 1 : 1 : 1 : 1 is expected.

Reference may now be made to other types of heredity, some of them related to those already considered. There are rare genes for abnormalities carried in the Y-chromosome. A number of them are recorded in this book. Figure 6 is such a pedigree of male-sex-linked hypertrichosis of the ears, with eleven cases, all males, in five generations. The Y-chromosome is the only vehicle which can account for this transmission only from father to son, never entering the female line at all. The transmission is also known as *holandric* and the condition is hemizygous, because the gene in the Y-chromosome has no mate. Typically in such a family every son will be affected, because he gets an affected Y-chromosome. The male twins in the fifth generation of this pedigree were too young to show the condition. Cases will be mentioned later, in which crossing-over from the Y- to the X-chromosome led to transmission of such a condition by a female.

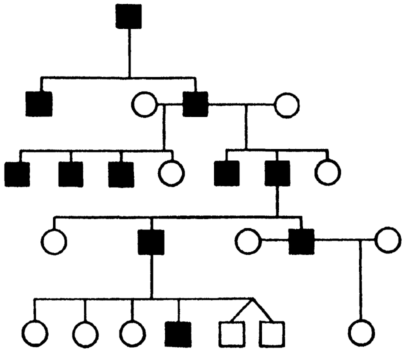

Fig. 6. Pedigree of male-sex-linked hypertrichosis of the ears. (After Tommasi)

As regards *crossing-over*, which is a widespread phenomenon in plant and animal genetics, one may say that it consists essentially in a pair of chromosomes in meiosis (reduction division) which are closely twisted about each other undergoing a break and exchange of segments at certain points. As a result, genes are transferred in large blocks from one chromosome to its mate, or even in rare cases to a chromosome of another pair (translocation). For a critical summary of problems of crossing-over see Mather (1938). Figure 7 illustrates another case of inheritance apparently in the Y-chromosome. Fusion of the radius and ulna in both arms (see p. 14) began with II. 2, presumably as a mutation in the Y-chromosome, his father and brother being normal. His eleven male descendants all have the condition, except in one family of the fourth generation. This family has two affected sons, one normal son and an affected daughter. This sibship can be explained on the assumption of crossing-over from Y to X in the two germ cells of the father (III. 8) which produced his affected daughter and normal son. The condition must also be dominant, since the daughter will have a normal as well as an affected X. Other cases will be discussed in later chapters, in which a gene in the Y-chromosome generally remains there but occasionally crosses-over to the X. Such a gene is not hemizygous, since it presumably has a mate (allele) in the X-chromosome, unless perchance the crossing-over is unequal. It appears that most of the genes in the Y, but apparently not all of them, are capable of crossing-over to the X. Haldane (1936) suggests that genes in the Y-chromosome may have been translocated from autosomes, but it seems more likely that the Y, in its earlier evolution, was emptied of many of its original genes.

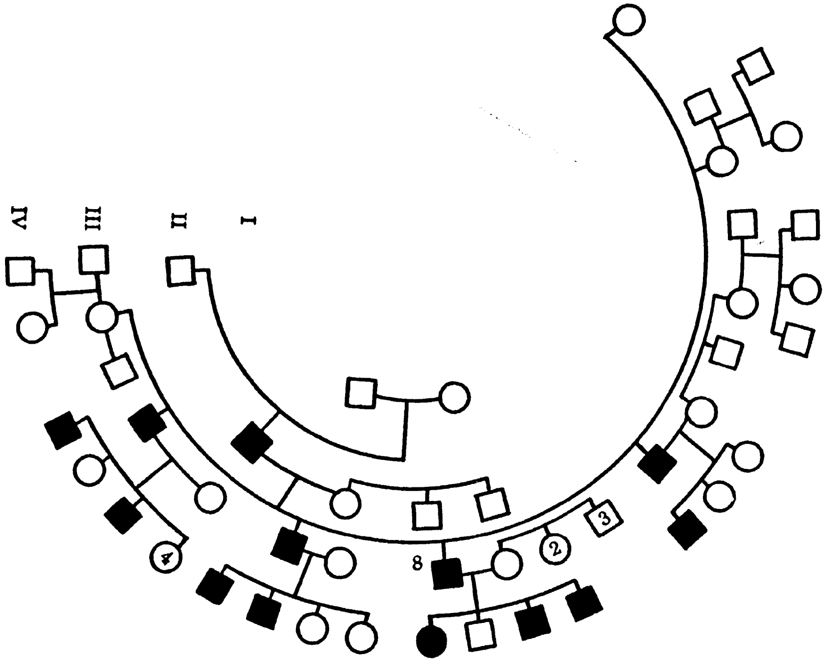

Fig. 7. Pedigree of bilateral radio-ulnar synostosis, probably in Y-chromosome with rare crossing-over to X. (After Davenport, Taylor and Nelson)

Many human genes are strictly dominant, one parent of an affected child always being affected. This was the case with the Chinese pedigree of optic atrophy in Fig. 2. But in other pedigrees of optic atrophy, such as Fig. 8, the same condition is an irregular or conditional dominant, i.e., certain individuals may transmit the condition without themselves showing it. Figure 8 has two such cases in which a normal mother with an affected sister transmitted the condition without exhibiting it herself. Although both their parents were normal, one of these parents also must have been a transmitter of the condition. The conception of conditional dominance was introduced by Levit (1936), who emphasized the frequency of dominant abnormalities in man. He and his colleagues concluded that the following are conditioned dominants: Basedow's disease, ulcus ventriculi, leukemia, eunuchoidism, bronchial asthma, goitre, paroxysmal tachycardia and probably pernicious anaemia and hypertonus, i.e., they occasionally skip a generation. From a survey of general works on human diseases, Levit found 38 conditional dominants, 14 recessive and 3 which he classed as intermediate. Similarly Cockayne (1933), in a comprehensive work on the inheritance of skin abnormalities and diseases, found 80 dominant, less than 20 recessive, 9 in the X-chromosome (7 recessive and 2 dominant or intermediate) and 4 in the Y.

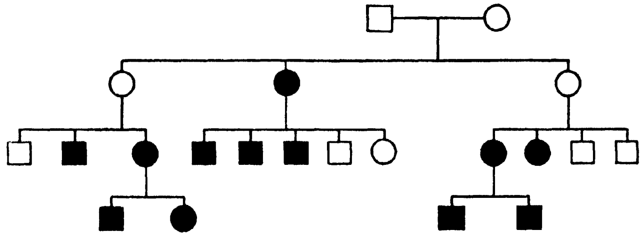

Fig. 8. Irregular dominant pedigree of optic nerve atrophy.

Many cases are now known in which the same abnormality is strictly dominant in some pedigrees and sometimes skips a generation in others. Several explanations of this phenomenon of skipping a generation have been offered. It is now known as *lack of penetrance*, which has become a very important principle in human genetics. Penetrance is an all-or-none reaction. The gene is present in the germplasm, as shown by its transmission to the next generation, but for some reason it has completely failed to express itself in the soma. The "battle of the genes" results in its defeat at an early stage of development. The term *normal overlaps* has been used for this condition, particularly in animal experiments and especially where the gene-expression shows a series of stages between fully affected and normal. In some cases the difference between strict and conditional dominance seems to lie in a difference of strength in the gene itself. In other pedigrees it seems that out-crossing brings in new genes which affect the dominance, changing it from a regular to an irregular dominant. Generally, however, a dominant pedigree appears to be persistently of one type or the other, and the percentage of penetrance is characteristic of the particular gene. For instance, the blood groups always show 100 per cent penetrance, in diabetes mellitus the penetrance is *ca.* 10 per cent and in leukemia a fraction of 1 per cent.

Related to penetrance is *expressivity*, which means the degree to which a particular gene expresses itself. Many genes are quite uniform in expression in all the affected members of a pedigree, but many others are highly variable. Polydactyly is quite uniform in some pedigrees, but in others the extra finger shows all stages of reduction until it is no bigger than a wart in the position where the extra finger should be. This variability is especially true of the hereditary *syndromes*, a medical term for a condition which expresses itself in apparently unrelated effects on several different organs of the body (see Chap. XVIII). Frequently one, two or more of these effects fail to appear in some individuals. One may show A, B and C, another A and C, a third B and C, a fourth only B and a fifth only A. These partial expressions are known as *formes frustes.* If a single gene is concerned, the syndrome is an extreme example of variable expressivity. Many of the inherited abnormalities with a physiological basis also show wide variation in expressivity.

A gene which has different effects on different organs of the body is said to be *pleiotropic.* The condition of multiple effects is called *pleiotropy* or *polyphany.* The genes for some of the inherited syndromes produce a variety of multiple effects. For instance, in Eddowes' syndrome the sclerotic coat of the eye is blue instead of white, the bones are so brittle that they easily fracture and otosclerosis (producing deafness) is frequently present. These are all concerned with mesodermal structures, but sometimes even derivatives of different germ layers are affected in a single syndrome which appears to be monogenic.

Another peculiarity of human genetics which was formerly emphasized (Gates, 1929) is that the same abnormal character may be dominant in one pedigree, recessive in another and sex-linked in a third. This triple method of inheritance is now known for many human abnormalities, but it seldom occurs in other organisms.[5] Why this should be so is not clear. These different forms of inheritance are found, for instance, in Leber's optic atrophy, night blindness and cataract, to take three cases from the eye. They are all contemporary, and there is no evidence that one form of heredity is being transformed into another. For one condition the dominant pedigrees may be most numerous, for another the recessive or sex-linked pedigrees may be most frequent. Certain characteristic differences sometimes occur between the genes for the same abnormality when they exhibit these three different methods of inheritance. Of course it is clear that in a sex-linked pedigree the gene is located in the X-chromosome. If the same gene is an ordinary dominant or recessive it must be located in an autosome (ordinary chromosome). The dominant and recessive forms of an abnormality are very rarely found in the same pedigree, so it is not known whether they are alleles, i.e., different mutations in the same chromosome locus, but on general grounds it seems probable that they frequently are. The dominant and recessive forms of spastic paraplegia, however, are not allelic (p. 1023) since the latter shows partial sex-linkage while the former does not. In the rumpless fowls of Dunn and Landauer (1936), dominance was gradually changed to recessiveness by crossings with normal — apparently through the accumulation of modifiers.

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[5] Castle showed that in rabbits dominant English spotting is closely linked (not allelic) to recessive Dutch spotting. In mice, Keeler (1931) found that dominant and recessive spotting are separate genes not linked. Fortuyn (1939) obtained a mutation with dominant spotting from a strain of mice which was heterozygous for recessive spotting. Dominant and recessive piebald patterns are found in horses. A few cases of similar dominant and recessive phenotypes occur in the experimental genetics of Drosophila. In sheep there are both dominant and recessive genes for black. In Drosophila, bent wing and cubitus interruptus (ci) are both dominant and recessive. These dominants are both lethal in the homozygous condition. In man, such conditions are generally known only as heterozygotes, but there is evidence that telangiectasis and brachyphalangy are dominant homozygous lethals and the same is probably true of many other "dominant" abnormalities. Dubinin found that cubitus interruptus in chromosome IV of Drosophila changes from recessive to dominant in the presence of any translocation between chromosome IV and the Y. Recessive vestigial also may become more or less dominant in the presence of various deficiencies, inversions and translocations (Goldschmidt and Gardner). These are generally regarded as *position effects* (see below). Stern (1943) has shown that with one, two or three doses of the ci gene the phenotype becomes cumulatively more like the normal. If one ci is present with the normal allele its action may become antagonistic rather than cumulative, the recessive condition thus changing to dominant. An explanation is suggested, based on different relative amounts of substrate on which the gene acts. Stern and Schaeffer (1943a) tentatively make a further analysis of gene action, based on their combining power with the substrate and their relative efficiency.

It is possible that the dominant or recessive gene may sometimes become sex-linked by simple translocation to the X-chromosome, and there is some evidence that the reverse translocation, from the X to an autosome, may (rarely) occur; certain possible cases are cited in later chapters, and Burks (1937) refers to an indication of the translocation of the gene for color-blindness from the X to an autosome. Considering the relative rarity of all such translocations and the frequency of sex-linked abnormalities, it seems more likely that these arise as mutations in the X-chromosome itself. This hypothesis, however, leaves the difficulty that the same gene arises in different chromosomes, where the substratum would be expected to be different. We have already pointed out that some recessive genes are known to be deletions and some dominant genes duplications of a small segment of a chromosome. Whether this principle will apply to the dominant and recessive allelic or pseudo-allelic genes in man is unknown.[6]

[6] In New Zealand Romney sheep a birthcoat having abundant "halo-hairs" is designated as the N-type. Dry (1944) has shown that N is inherited as a simple dominant in two independent stocks, a simple recessive in a third stock derived from one of them; and selection has produced a type in which N is multifactorial. The horns of these three strains have corresponding relationships. Dry suggests the three hereditary forms of N are in a sense allelic, the dominant form representing duplication of a gene, the derived recessive form the loss of the duplicate gene (i.e., reversion to a single gene, perhaps through unequal crossing-over), multifactorial N representing another derived genic condition. This hypothesis may apply to the many cases of dominant and recessive genes for the same condition in man.

We know but little regarding the origin and evolution of chromosomes in lower organisms, but since in some of the primitive blue-green Algae (Cyanophyceae) the chromosomes divide transversely, although in higher members they divide longitudinally, we have suggested (Gates, 1932) that the axis of each chromosome throughout its length was originally uniform (but different from the other chromosomes), the latter becoming differentiated by mutations in segments of a chromosome. Such differentiations would "necessitate" longitudinal division, to maintain stability. The resultant "genes" would in this way ultimately reach the minimum size, i.e., the length of a protein molecule, as appears to be the case in all the more highly evolved organisms, from insects to man.

It has proven to be a general rule, though not without exceptions, that the recessive form of a disease or abnormality is the most virulent or extreme, the dominant form the mildest, and the sex-linked form intermediate. The greater virulence of the recessive condition is frequently expressed by earlier onset, as indicated by Bell and by Levit in certain cases. The explanation, as William Allan (1937) points out, lies in the fact that in the dominant form the affected individual is heterozygous, the defective gene being matched with a normal allele, whereas in the sex-linked form the gene is generally hemizygous, having no corresponding gene in the Y to partly neutralize its effect. In the recessive form, the gene is intrinsically weaker than in the dominant form, since in the heterozygous condition it produces no effect. Nevertheless, the presence of two genes reinforcing each other in the nucleus, with no normal neutralizing gene, produces a stronger effect than a single slightly stronger gene balanced against a normal in the dominant heterozygote. These relationships can thus be largely rationalized on the basis that the dominant and the sex-linked form are the same gene in different loci, whereas the recessive gene, probably in the same locus as the dominant, is somewhat weaker in its effect when single, so that it fails to reach expression — it lacks penetrance except in the homozygous state. This makes it useful to introduce the conception of a *threshold for penetrance* in each type of gene in a certain gene milieu or genotype. This conception is of general application in genetics.

There remains a difficulty, however, with the sex-linked gene. If it were simply the dominant gene translocated, then heterozygous females should show the condition, whereas they are generally normal, although, as this book will show, variable dominance in the female is characteristic, not only of color-blindness and hemophilia but of other sex-linked characters as well. There is, however, another principle of genetics known as the *position effect*. In a few cases both in animals and plants it has been shown that the effect of a gene is altered when it is translocated to a new chromosome with different genes as neighbours,[7] although when transferred back to its original position the gene itself is unchanged. It is therefore possible that the dominant gene when transferred to the X-chromosome might show a change in strength, which is equivalent to a change in dominance. However, this explanation is purely hypothetical at present. Some evidence will be adduced later for the view that genes which can be thus transferred between the X and an autosome are near the end of the X, in which position they might gain in strength through having neighbours on only one side.

On this basis it might be supposed that the recessive gene could also be translocated to the X, in which case there should be two kinds of sex-linked genes for a given character, one stronger than the other. At present there is no clear evidence of this, although some forms of hemophilia are much more severe than others (see Chap. XIV), and genes essentially similar to that for hemophilia may be either dominant or recessive in inheritance. As the chromosomes are all highly differentiated, it would appear probable that the dominant, recessive and sex-linked forms of a particular abnormality all arise originally from the same locus. On the other hand, many very similar mutations in Drosophila arise from quite different loci. Bunak has proposed the useful term *isophenic* for genes which have similar phenotypic effects. The term *heterochromatin* refers to the more deeply staining portions of chromosomes, which appear to carry proteins of less complex type. These portions have frequently been regarded as inert (i.e., containing no genes) or even degenerate. The supernumerary chromosomes of maize and sorghum (in addition to the ordinary diploid set) also stain deeply and have no marked effect on the plant, even when several are present. The Y-chromosome in animals also appears generally to have very few genes.

On the basis of facts such as these, and an analysis of the relation of the Y-chromosome in different stocks of *Drosophila melanogaster* to the quantitative inheritance of the sternopleural chaetae, Mather (1944) presents the view that while the euchromatin is concerned with the major genes of ordinary Mendelian type, the heterochromatin regularly carries the polygenes, i.e., multiple quantitative genes which are cumulative in effect. The genes in the Y-chromosome would then be mainly polygenes, crossing-over with similar genes in the X. These quantitative genes, many of them scattered through smaller heterochromatic areas of the autosomes, would thus serve to maintain a more delicate balance of the species than is possible with the major genes alone. On this view the qualitative and quantitative types of gene are complementary in effect and "embedded" in different kinds of chromatin. It remains for the future to disclose how widely this interesting hypothesis will hold in organisms.

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[7] Recent work indicates that the position effect may be in relation to the adjacent heterochromatin. Some position effects may result from gene competition (see Stern and Heidenthal 1944).

By way of contrast, Pontecorvo (1943) suggests that heterochromatin results from the grouping of similar genes, the euchromatin from intermingling of dissimilar genes. He believes that the X- and Y-chromosomes in mammals differ from each other and from the autosomes in their nucleic acid cycle. He suggests that the evolution of the X and Y in mammals consists in progressive specialization, the differential segment of the X coming to carry mainly female-determining genes, the pairing segments of X and Y carrying male-determining genes. This would explain the rarity of sex-linkage in mammals, but in man many sex-linked abnormalities are now known. Morrill (1945) records that in a herd of Hereford cattle in Utah an extra toe on each forefoot is inherited as a simple sex-linked recessive.

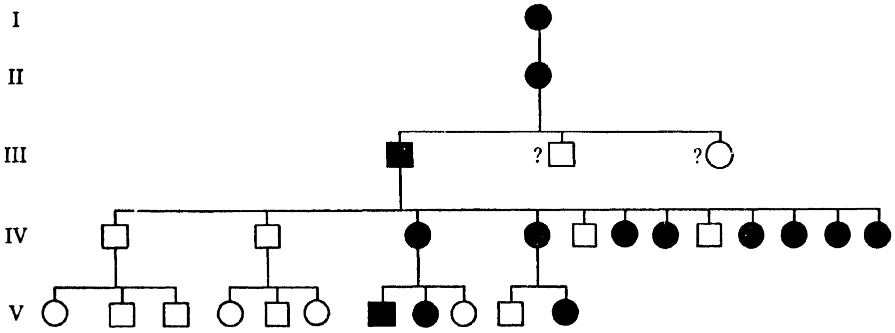


Fig. 9. Dominant sex-linked pedigree of faulty enamel. (After Bampton)

Leber's optic atrophy occurs in the triad of dominant, recessive and recessive sex-linked forms (see p. 215), but many of the pedigrees of this disease show exceptions to any of these types of inheritance. In some quite extensive pedigrees of optic atrophy and some other conditions it is practically impossible to determine whether the condition is dominant or sex-linked. Nystagmus also shows the triad of types of heredity. Figure 8 (p. 15) is the pedigree of an irregular *dominant* family. Dominant sex-linked genes are rare and one of the few is given in Fig. 9, Bampton's (1914) pedigree of faulty enamel and dental discoloration. It will be seen that all the daughters and none of the sons of an affected father (III. 1) are affected. This is because the daughters all receive the father's X containing the dominant gene, while all the sons receive his Y instead. Heterozygous mothers (IV. 3, 4) transmit to half their sons and half their daughters.

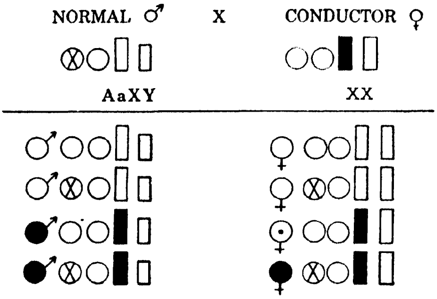
Usually in this type of pedigree the dominance is incomplete or variable in the female sex.

In a dominant sex-linked pedigree all the daughters of an affected father will be affected since they receive his X-chromosome, but he will never have an affected son. This is the only difference of such a pedigree from an ordinary autosomal dominant. But if crossing over from X to Y occurs even rarely, then this difference breaks down.

In another pedigree of Hemmes (Fig. 10, p. 22) the manner of inheritance differs in the descendants of two brothers. On the left the transmission is that of a dominant with 11 cases (6♂ 5♀) in three generations and only two skips. On the right this gene is transmitted as an ordinary sex-linked recessive, except that one woman is affected. It seems necessary to assume here that the gene had been translocated from an autosome to the X in one germ cell of the father of I. 2. If this is so, it helps to confirm my hypothesis of the relation between the dominant and sex-linked forms of inheritance, the latter arising from the former through translocation.

Punnett (1933) offers another explanation, which probably applies to a number of cases, although not to the one above. He points out that numerous eye abnormalities, such as megalocornea, night-blindness, microphthalmia, zonular cataract, macular degeneration, and myopia, which are dominant in some pedigrees and sex-linked in others, also show exceptions to either rule in some families. For example, Fig. 11 is another pedigree of nystagmus, which Waardenburg regards as an irregular dominant. There are 19 cases (13♂ 6♀) in four generations, but in sibships the normals number 56 : 19 affected. Normal females are frequently transmitters, and Punnett regards this as a sex-linked recessive pedigree in which an inhibitor for normal is also present in an autosome. In the presence of this inhibitor the recessive character would appear dominant, and this would account for the six affected females. This hypothesis is based on the analogy of dominant white color in poultry, which is due to an inhibiting factor. The whole pedigree shows 13 ♂ : 25♂ : 6 ♀ : 31 ♀.

Using Punnett's symbols, we have



giving offspring

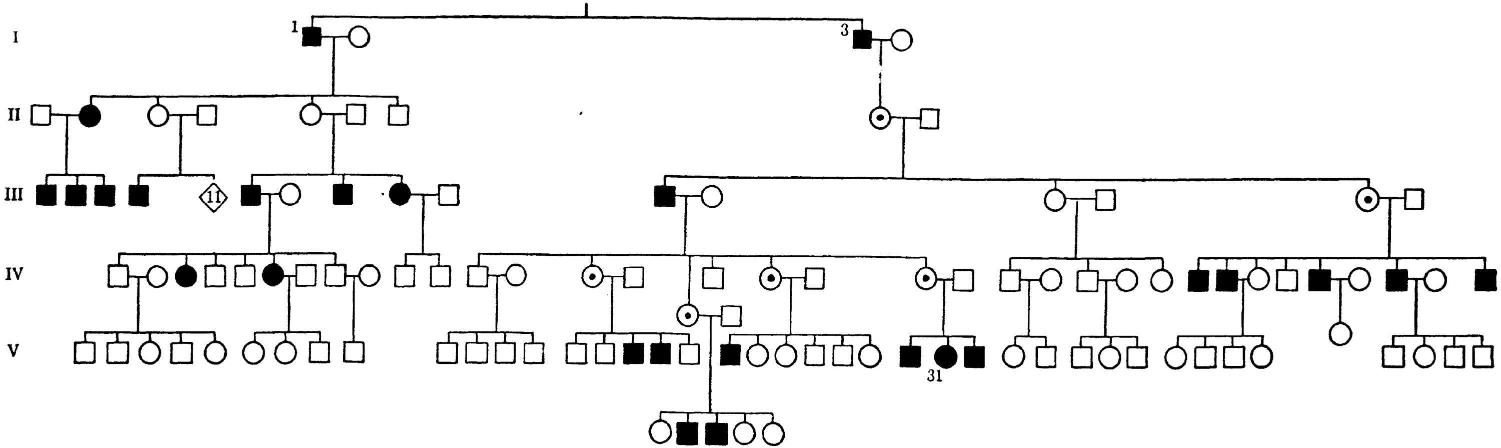


Fig. 10. Hemmes' pedigree of nystagmus. See text.

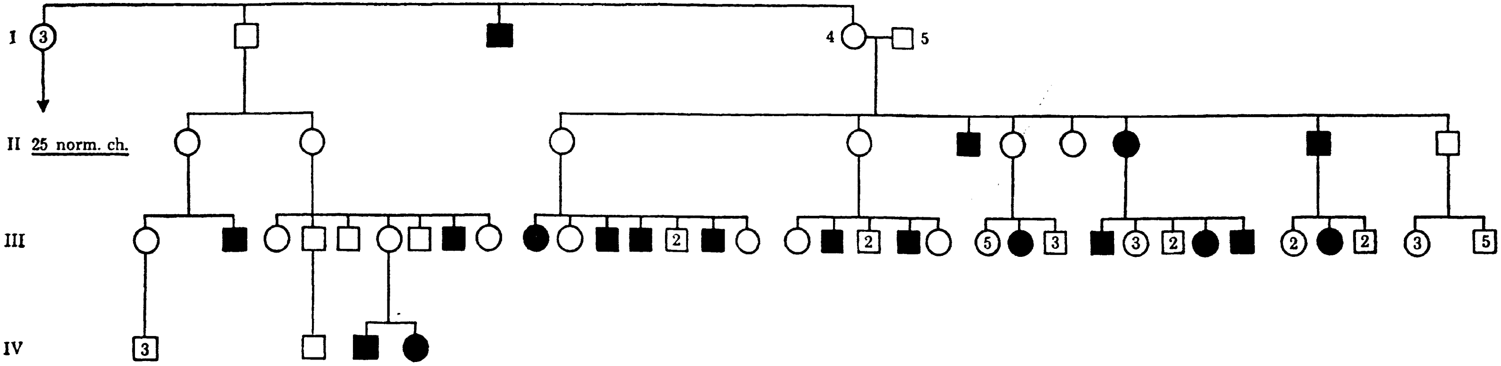
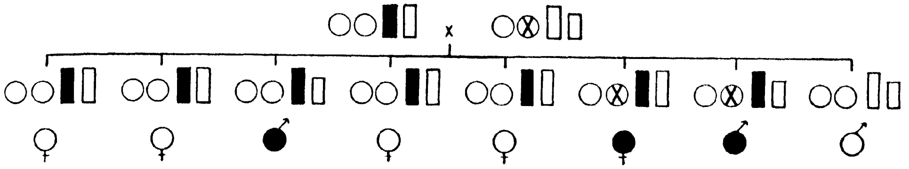


Fig. 11. Irregular dominant pedigree of nystagmus.

A is a gene in an autosome which, in effect, changes the gene in X from recessive to dominant by suppressing the normal. Thus from a cross between a normal man carrying the inhibitor, and a woman who is heterozygous for (recessive) nystagmus but normal, 50 per cent of the sons and 25 per cent of the daughters will be affected and another 25 per cent of the daughters will be carriers. Applying these symbols to I. 4, 5 and their eight children in Fig. 11, we have



i.e., 2 ●♂ : 1 ♂ : 1 ●♀ : 4 ♀ where the expectation is 2 ●♂ : 2 ♂ : 1 ●♀ : 3 ♀, and similarly for the rest of the pedigree.

If (+) represents the inhibitor, there will be sixteen possible matings, with results as in Table 1.

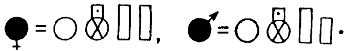
TABLE 1

VARIOUS RESULTS OF A SEX-LINKED RECESSIVE GENE COMBINED WITH AN AUTOSOMAL INHIBITOR

	♂	●♂	♀	♀̇	●♀
1. ♀ × ♂	All	—	All	—	—
2. ♀ × ♂ +	All	—	All	—	—
3. ♀ × ●♂	All	—	1	1	—
4. ♀ × ●♂ +	All	—	—	1	1
5. ♀ + × ♂	All	—	All	—	—
6. ♀ + × ♂ +	All	—	All	—	—
7. ♀ + × ●♂	All	—	—	1	1
8. ♀ + × ●♂ +	All	—	—	1	3
9. ♀̇ × ♂	1	1	1	1	—
10. ♀̇ × ♂ +	2	2	2	1	1
11. ♀̇ × ●♂	1	1	—	1	1
12. ♀̇ × ●♂ +	2	2	—	1	3
13. ●♀ + × ♂	2	2	2	1	1
14. ●♀ + × ♂ +	4	4	4	1	3
15. ●♀ + × ●♂	2	2	—	1	3
16. ●♀ + × ●♂ +	4	4	—	1	7

In the table, matings 13–16, the mother is affected. In ordinary recessive sex-linkage affected females are homozygous and all their sons will be affected. But when the affected condition is produced by an inhibitor for the normal gene, only half the sons will be affected. Thus normal sons can be produced by affected mothers.

On this interpretation, three women in Fig. 11 married men heterozygous for the inhibitor, which implies a relatively high frequency for the inhibitor.

Punnett also points out that if the gene for such a condition as night-blindness is near the end of the X-chromosome, it might become detached therefrom and attached to the end of an autosome carrying the inhibiting factor. The defect would then behave as a simple dominant, since the inhibitor for normal is in the same chromosome. The symbols would be,  If there was crossing-over, a chromosome might be formed which contained the defect without the inhibitor. Such apparent normals carrying the inhibitor would produce some defective individuals with power to transmit to some of their children. If translocation can take place from an autosome to the X, of which we have already had some evidence, it is equally probable that it can occur in the opposite direction, and Punnett's hypothesis is applicable to a number of pedigrees.

It is evident, however, that all sex-linked genes cannot be near the end of the X, so that some sex-linked anomalies should be known only in sex-linked and not in dominant or recessive form. This is true of color-blindness and hemophilia, in both of which large numbers of extensive pedigrees have been published. Only one pedigree of a weak form of bleeding shows autosomal inheritance (see Chap. XIV).

Pedigrees of dominant sex-linked characters, such as those which have already been referred to, are rare, and the dominance appears always to be irregular. Sex-linked characters are nearly always recessive, and, as already mentioned, the dominance is variable in the female. Why the majority of autosomal genes should be dominant while most sex-linked characters are essentially recessive is not clear. On the translocation hypothesis we should expect the recessive genes to be the ones which have been most frequently translocated to the X. But as the difference between dominant and recessive must now be recognized as purely relative, these comparisons have no very stable basis.

In the case of so-called sex-linked recessives, it can now be recognized that the recessiveness in the female is often incomplete, so that the line between dominant sex-linked and recessive sex-linked pedigrees is by no means sharply marked.

We have already seen that a character may be strictly dominant in some pedigrees, but show irregular dominance in others. This lack of penetrance moreover occurs in many degrees, so that a dominant pedigree with a low degree of penetrance may be difficult to distinguish from a recessive pedigree. Even some strictly recessive genes may show only 70 per cent of penetrance in the homozygous state. Thus we see that in human genetics the old sharp distinction between dominant and recessive completely breaks down and we have instead a sliding scale, from strict dominance with never a skip at one end, to recessive characters showing incomplete penetrance at the other. Many genes for abnormalities also show great variation in expressivity.

Besides the many cases of irregular or conditional dominance — frequently conditioned by the presence of other genes or inhibitors or by the genome as a whole — there is also reversed dominance. The boy of five with curly hair sometimes develops into a man of twenty-one with straight hair. Less frequently the reverse change takes place. Every character in fact represents a moving equilibrium from birth to senility and to be fully understood must be studied in all its changing relations throughout life. Children resemble one parent more at one stage of development and shift toward the other in various features at a later stage, as the tides of heredity ebb and flow.

Lack of penetrance in a dominant character leads to its appearance among siblings in less than a 1 : 1 ratio. This has sometimes led to the assumption that two or more independent genes were involved in producing the character. Since reduced penetrance alone, or the presence of an inhibitor, will widen the ratio of normal to affected, even a 15 : 1 ratio is not by itself sufficient evidence for postulating two genes instead of one, except as a possibility. There may be a few cases in which a dominant and a sex-linked gene co-operate in producing an abnormality, such as goitre, but strict polymery of two dominant or recessive genes has hardly been proven in connection with any human abnormality or disease. On the other hand, *polymeric factors* are well recognized for such racial features as skin color and probably they apply to head shape and nasal index, but apparently not to hair shape. The term *polygenic* is generally preferable to polymeric, as the latter implies that the genes or factors are alleles while the former does not. In numerous abnormalities to be considered in later chapters the sexes are unequally affected, the penetrance of the gene being more reduced in one sex than the other, as in the Laurence-Moon-Biedl syndrome. In many pedigrees the frequency of affected males is greater than of affected females. When the difference is very marked, it becomes a question whether it is due to difference in penetrance or to the presence of a sex-linked factor, as in goitre, in which the female is more affected.

Many inherited defects occur with greater frequency in one sex than in the other. Bell (1940) gives a list of diseases in which more males than females are affected, and another in which there is an excess of affected females, the ratio of male sex-incidence being given in each case. These lists are produced in Table 2.

TABLE 2

Excess of Males Affected

Hernia (inguinal)
Cancer of tongue, mouth, lip
Duodenal ulcer
Derangement of knee-joint
Cancer of the thorax
Cancer of the oesophagus
Congenital pyloric stenosis
Papilloma of the bladder
Peptic ulcer
Cancer of the bladder
Talipes
Menière's disease
Gastric ulcer
Papilloma of larynx or tongue
Cancer of the stomach
Cancer of the rectum
Asthma (under 15 years)
Deviation of nasal septum
Pneumonia, broncho-pneumonia
Renal calculi
Rodent ulcer
Salivary calculi
Phthisis
Hirschsprung's disease

Excess of Females Affected

Adenoma of thyroid, goitre
Thyrotoxicosis
Congenital dislocation of hip
Gall-stones
Cervical ribs
Choleocystitis
Rheumatoid arthritis
Sydenham's chorea
Exostoses
Femoral hernia
Lipomata
Mitral stenosis
Migraine
Splenic anaemia
Diabetes mellitus (over 29 years)
Trigeminal neuralgia
Diabetes mellitus (all ages)
Hyperpiesis
Rheumatic carditis
Tubercular adenitis or abscess
Myasthenia gravis
Diverticulosis
Rheumatism
Tubercular spondylitis
Disseminated sclerosis
Enuresis

The percentage of affected males in the left-hand column ranges from 86.47 (hernia) to 56 (Hirschsprung's disease), that in the right-hand column from 11.46 (goitre) to 44.91 (enuresis). Some of these divergencies are related to anatomical, endocrine or "environmental" differences in the sexes. In other cases the reason for the difference is not clear. The sexes are found to be about equally affected in the following: syringomyelia, bronchitis, cancer of the colon, harelip and cleft palate, diabetes mellitus (under thirty years), sinusitis, paralysis agitans, otitis media, arthritis, umbilical hernia (under fifteen years), bronchiectasis, pernicious anaemia, congenital heart disease.

From the cases already cited, we have seen that sex-linkage takes various forms. The gene may be dominant or recessive. It may be (1) in a part of the X which is non-homologous with any part of the Y, (2) in a part of the X which is homologous with a portion of the Y, in which case it is *partially sex-linked*, (3) in the non-homologous portion of the Y, producing holandric or male-to-male inheritance. These conditions will be further discussed in Chap. IV. Snyder (1942) has discussed them, with numerous examples from human heredity.

Sex-limited inheritance, as in the well-known instance of horns in sheep, which are confined to the males in certain breeds, is an extreme difference of penetrance in which horns are present in all males and absent from all females. This may also be regarded as a difference in dominance, horns being dominant in the male and recessive in the female. Ibsen and Cox (1940) show that in some breeds of sheep which produce scurs the situation is complicated by modifiers. Warwick and Dunkle (1939) show by crosses of Dorset and Rambouillet sheep that there are three alleles, **H**, **H**^{I} and **h**, for horn, **H** being the hornless condition. Blunn (1943) shows that some Navajo rams have four horns and some ewes none.

No human racial character is known to be sex-linked, but there is some evidence for a sex-linked factor which makes brown eyes more frequent in women than men. Apparently the only sex-limited [8] character known in man is baldness. It has been shown (see p. 340) that baldness is due to an autosomal gene which is dominant in men but recessive in women, so the latter only become bald as a rule when they are homozygous for the gene. Figure 12 is a pedigree showing this form of inheritance. It includes three women who were homozygous and bald, three others who were heterozygous having thin hair. A daughter may be expected to transmit baldness from her father to half her sons.

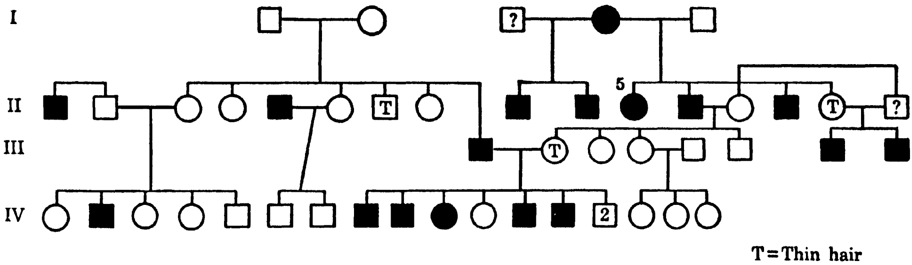


Fig. 12. Pedigree showing inheritance of baldness.

Federley described a case in Lepidoptera of the genus Pygaera, in which malignant tumors appear in the male larvae (which are XX in sex-chromosome constitution, the females being XY) and are confined to the male sex. The explanation given for this (see p. 1187) is that the Y-chromosome of the females contains a gene which stimulates the triploid polar nucleus of the egg to divide and form tumors.

Another rare form of inheritance is that in which the character is transmitted only from mother to daughter in the female line. This is *hologynic* inheritance. Such a pedigree of color-blindness was published by Cunier in 1839 (see p. 142) and is shown in Fig. 13. L. V. Morgan (1922) discovered this type of inheritance in Drosophila and showed that it was due to the attachment of the two X-chromosomes in the females. Since then, seven strains with attached XX's have been reported (Morgan, 1938). Four arose from sperm carrying attached XX's, two of these males being father and son. Mrs. Morgan shows that in at least one strain the attached XX's arose by two steps of crossing-over between the X and Y in males, the two arms of the Y being thus replaced by X's. Twelve females were found to have received separate XX from the male, and about 0.2 per cent of the sperm are known to carry XX. Only two in fourteen cases showed XX (attached X's). As explained on p. 143, some of the offspring in such strains are XXY. The "dominance" of the color-blindness in the women of Cunier's family would be explained by the presence of two attached X-chromosomes, each carrying the gene for color-blindness, so these women would be homozygous for it. It is highly probable that XXY females occur in man, and they could be discovered through hologynic inheritance of some sex-linked character.

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[8] Better called sex-influenced.

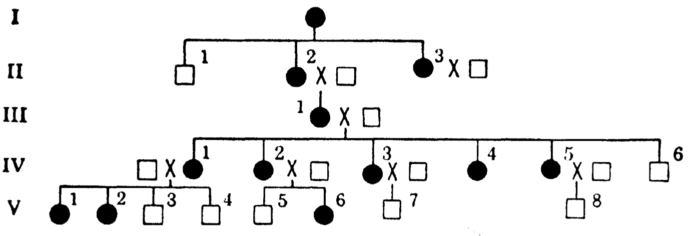

Fig. 13. Hologynic inheritance of color-blindness.

It is probable (see Chap. III) that triploid and tetraploid human beings will some day be found, although they are certain to be rare and they will not necessarily be of larger than normal size. They might be discovered through peculiarities in their genetic behavior. Triploid organisms are generally sterile.

It was formerly supposed that any human pedigree could easily be recognized as showing dominant, recessive or sex-linked inheritance, but the recognition of lack of penetrance blurs the sharp distinctions between these categories. In many short pedigrees in this and later chapters the type of inheritance can only be stated with more or less probability and not with absolute certainty. Levit (1936) treats as sex-linked only pedigrees in which at least nine sons of affected fathers were normal. This is based on the fact that if the gene is autosomal the chance of such a result would be $\frac{1}{2^9}$ or 0.00195, which corresponds approximately with 3 σ, which is accepted as statistically significant. This, however, is not an adequate measure of such a pedigree, because the larger the number of affected males (with or without children) the higher the probability of sex-linkage. In practice, many pedigrees will be recognized as sex-linked recessive when no single case of an affected (homozygous) female has occurred. With rare sex-linked genes, affected females are only likely to arise after intermarriage of relatives.

When an anomaly is more frequent in one sex, this has often been ascribed to sex-linkage, but it may also be due to a higher degree of penetrance of the gene in one sex. Fisher devised a statistical method of testing this situation, and Csik and Mather (1938) applied it to Sjögren's data on oligophrenia, Macklin's on the Laurence-Moon-Biedl syndrome, Sanders' on harelip and cleft palate[9] and Zieve, Adkinson and Balyeat on allergy. If sex-linkage is the cause of the excess of affected boys, then the excess should be confined to the sibs of affected boys and fail to appear among the sibs of affected girls. The method was applied also to albinism, which is somewhat more frequent in males, but the kind of excess which should result from sex-linkage failed to appear, showing that it is an autosomal recessive, as generally recognized. Applied to Bell's 368 families with color-blindness, among the sibs of affected boys there were 907 affected boys : 98 affected girls (9.3 : 1), whereas among sibs of affected girls there were 97 affected boys : 124 affected girls, thus amply confirming the sex-linked character of color-blindness. By the same method, none of the four conditions mentioned above showed evidence of sex-linkage. In the case of allergy the result was not clear, as there was an excess of affected girls in two sets of data and of affected boys in the third set. In the case of the Laurence-Moon-Biedl syndrome the ♂ and ♀ sibs of affected boys show equal frequency, but the brothers of affected girls show the character with twice the frequency of their sisters. Harelip, on the other hand, showed an excess of affected among brothers as compared with sisters of both affected sexes. There are many other cases to which this method could be applied.

The distribution of sex-linked genes in a population can be determined. If **A** is the normal and **a** the recessive sex-linked gene, then the frequency is $p\mathbf{A} : q\mathbf{a}$ in males, and $p^2\mathbf{AA} : 2\,pq\mathbf{Aa} : q^2\mathbf{aa}$ in females. If the proportion of affected females is greater than q^2, then the gene shows partial dominance in the female, if less than q^2 there is incomplete penetrance in the female. It will be seen also that the proportion of ♂ to ♀ bearers of the trait will be $q : q^2$, but this might be affected by differential viability.

We have thus far been dealing with definite genes for particular conditions, but this does not exhaust the possibilities of inheritance.

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[9] On the other hand, Bell (1940) found the sexes equally affected with harelip and cleft palate, 114♂ : 110♀.

There are some conditions in which it appears that the inheritance is not a definite gene but the *tendency* to produce a particular condition. For example, Wright (see also Chap. XXVIII) found a strain of guinea pigs in which otocephaly appeared with a frequency of about 1 per cent. Branches derived from this strain produced respectively 5 per cent and 27 per cent with fair regularity, the production of each monster being a chance event in the strain, not referable to a particular gene distribution. Similarly, taillessness is rare in laboratory rats, only 19 sporadic cases having appeared in 170,000 births; but certain lines differ from the general population in having the tendency to produce tailless young with a higher frequency. Dunn (1941) describes a strain which produces 4 per cent tailless young. All possible matings, such as tailless × tailless, tailless × normal or normal × normal within this strain, give the same result, i.e., about 4 per cent with the defect. Evidently not a single gene but in some sense the genetic constitution as a whole determines that 4 per cent of the offspring will have the defect.

There are many cases in man which apparently belong to this category of inheritance, but in the absence of experiment they are often difficult to distinguish from simple genic effects. In some forms of cancer the inheritance may be of this type. The defect may be produced by the way in which the early intra-uterine environment impinges on the organism, and yet the tendency for it to appear in the strain is inherited. From this point of view it is a form of susceptibility; but it is a specific susceptibility, producing in one case various degrees of otocephaly and in another taillessness. The genetic constitution may be said to determine the threshold of response to a particular environmental condition arising *in utero* with rather uniform frequency. There is now much evidence (see Bauer, 1945) of the *constitutional biological inferiority* of particular organs, such as the stomach, heart or liver. Such weakness of an organ or structure is of genetic origin and renders it particularly liable to breakdown under disease or strain.

Sewall Wright's (1934) analysis of extra toes and their inheritance in guinea pigs leads to further points of view regarding the nature and history of certain types of gene in the germplasm. The guinea pig and all wild cavies have digits II, III, IV and V on their forefeet, but lack the thumb. On their hind feet they have II, III and IV, but lack both the big and little toe. Castle produced by selection a strain in which the little toe was constantly present — the re-emergence of a gene condition which had been lost for millions of years. Wright showed that no single gene is responsible for little toes, but that at least four approximately equivalent genes are necessary. The development of the little toe requires a combination of favorable genes in order to pass a certain physiological-embryological threshold. Near this threshold environmental factors have important effects which may be indistinguishable from genic effects, as shown by the high correlation between litter mates. Young mothers and unfavorable feeding conditions also produced a high incidence of little toes. Environmental factors can thus act as general modifiers of the developmental pattern. The multiple hereditary defects occasionally found in a child sometimes appear to have a similar basis, unfavorable prenatal conditions having permitted several genes to produce their effects when under more favorable conditions they would have been crowded out and unable to emerge.

In another guinea-pig stock, Wright obtained a mutation (Px) with rudimentary little toes, rudimentary thumbs and big toes, which behaved as a single semi-dominant gene with frequent irregularities. These animals were vigorous and pentadactyl, 7 per cent larger than the normal. In crosses with the previous little-toed strain, the little toes and thumbs were well developed and the tendency to develop big toes was greatly strengthened. Results of this kind, in which one factor affects the development of another, lead to the conclusion that the apparent localization of effects of these factors depends on "the relational pattern of the organism as a whole at the time at which they are brought into play, rather than on any specific relation between particular factors and particular morphological entities," a view which is applicable to certain human abnormalities.

When the Px strain was inbred it produced about 25 per cent of monsters homozygous for the defect, which usually die *in utero.* Their legs are short and distorted, the feet like broad paddles with seven to twelve undifferentiated digits. The head is also misshapen, the eyes rudimentary, the brain often protruding and clefts present resembling harelip. Harelip and polydactyly or syndactyly also sometimes appear in children with multiple defects.

It is well known that in horses the evolutionary loss of toes has gone farther than in any other mammal, yet polydactyly still occurs in horses as a very rare abnormality. Julius Caesar's horse and Alexander's were polydactylous (see Gates, 1929, p. 166). As in guinea pigs, the genic basis for extra toes has been thrust into the background of the germplasm, far below the usual threshold, and yet it has not been annihilated, which shows the surpassing conservatism of the germplasm. Stockard showed that a similar condition exists with regard to the toes of dogs.

There is now extensive evidence of the inheritance of *susceptibility* to certain diseases in man, i.e., to the attacks of bacteria and viruses. Although innumerable cases of an inherited factor for susceptibility or resistance to a particular bacterium or fungus are known in animals and plants, the medical profession has only tardily realized the importance of inherited resistance in man. The subject is discussed in Chap. XXVII. Recent evidence appears to show that susceptibility to poliomyelitis depends on a single recessive gene, and there is also evidence that the susceptible child has certain recognizable constitutional features, although these are not yet fully defined. Rheumatism and related conditions appear to be partly a matter of susceptibility to certain infections, and the blond type is considered by some to be more susceptible. In tuberculosis, susceptibility is generally recognized to be connected with the asthenic type of constitution or body build, and there is evidence that some races are more susceptible than others to tubercle and also to tetanus. Certain families are shown to be highly susceptible to pneumonia. That inherited resistance and susceptibility are strong factors in connection with leprosy is not generally recognized, but the evidence is now extensive (see Chap. X). Susceptibility as an element of inherited constitution is thus already of considerable importance. Body build, as another element of constitution, is discussed in Chap. XXVII, and recent important advances in this field are explained.

The sudden appearance of a new abnormality in several members of a family has been called by Siemens *heteropheny* or transformative heredity. It is doubtful, however, whether this involves anything more than the emergence of a recessive gene in several sibs from parents who do not show the character but may have other abnormalities. In some cases it involves a change from partial to full expressivity of the gene determining a hereditary syndrome.

What is known as *anticipation*, that is, the progressively earlier appearance of an inherited condition in successive generations, will be referred to later in connection with several abnormalities. Its existence has frequently been denied and in some cases it can be explained as a false statistical result arising from the fact that only those in whom it arises at a later age will live to reproduce (Davenport, 1916). This, however, is probably not the whole explanation. Nettleship (1909) accepted the law of anticipation and in fact named it, recognizing its existence in connection with certain ocular defects. Pieraccini (1932) points out that he had still earlier (1901) supported and illustrated the conception of anticipation in some diseases of the nervous system and of metabolism, but he denies the existence of homochronicity.

A well-authenticated fact is that *homochronous heredity* (onset at the same age, Vogt) is frequently characteristic of siblings. Macklin cites a number of cases, but there are others (relating to some diseases) in which the onset is at widely different ages. Thus it is clear that age of onset is important in many diseases, and that its relation to the disease varies widely in different cases. Different strains of the same disease may show characteristic differences in age of onset.

If the mean age of onset for *all* affected individuals of a pedigree is determined for successive generations, then no statistical fallacy is involved as regards "anticipation," and chance is excluded if several pedigrees of the same condition give the same result. Selection may, however, be at work if later age of onset is inherited. This law would naturally apply especially to dominant genes, and if it exists there is at present no biological explanation for it. Macklin (1932) cites a number of instances in which the law seems at first to hold, the defect appearing at successively earlier ages until in some cases it is congenital. For example, in pedigrees of progressive muscular atrophy the average age of onset in the first generation (6 cases) was 51 years, second generation (10 cases) 43.4 years, third (7 cases) 43 years, fourth (2 cases) 31.5 years, fifth (1 case) 13 years. This will only be significant, however, if all the members of the younger generations have already passed the likely age of onset, but the decreasing numbers of cases in successive generations indicates that this was not so. Polycystic kidney also provides what might be a significant case. The age of onset, when recorded, gave an average of 47 years for first generation cases (11), 29 years for second generation (21 cases), 25 for third (8 cases) and 14.5 years for fourth (2 cases). The large decrease in numbers affected, however, again leads one to suspect that the later generations would continue to produce other cases at older ages, thus vitiating the evidence. This criticism will also apply to single pedigrees. Theoretically they should all have lived out their life span before one can be certain that they will not experience the onset in old age.

What appears to be a well-authenticated pedigree of cataract with anticipation is referred to on p. 991. There may also be anticipation in connection with glaucoma. In Huntington's chorea (p. 1017) and similar conditions it has been suggested by Haldane that, through the selection of modifiers, the age of onset tends in the opposite direction, the disease having begun as an infantile condition and slowly progressing through the ages to a senile time of onset, but this is highly speculative. In the case of spastic paraplegia (p. 1023), Haldane found that the three characteristic ages of onset were due not to the action of modifiers but to three recessive alleles.

Retinitis pigmentosa occurs not only in dominant, recessive and recessive sex-linked pedigrees, but some authors recognize infantile, juvenile and later forms. There must be at least five different genes for retinitis pigmentosa, one an autosomal dominant, one a partially sex-linked dominant, one sex-linked and two or more recessive. According to Fraser Roberts (1940), the recessive gene which also causes deafness is the only one with a distinct clinical effect. He also points out that the proportion of consanguineous marriages between the parents of affected children is much too high to correspond to the frequency of the disease in the population. Hence different recessive genes must be involved. Collection of forty-one pedigrees from consecutive cases without selection gave one sex-linked and the rest recessive, but some of these were single cases, some of which may be non-hereditary. In dominant forms the age of onset is twenty-five to forty years and the condition less severe, rarely leading to blindness. The recessive sex-linked form begins at twenty to forty and complete blindness results at forty to fifty. In the severe recessive form the sight is affected in the first decade and the child is blind before twenty. Thus in retinitis pigmentosa the age of onset is a measure of the severity of the disease and an indication of the type of inheritance. There is also evidence of partial sex-linkage in this condition (see Chap. IV).

Allan (1937) shows that the same is true for peroneal atrophy of the Charcot-Marie-Tooth type. When dominant, the onset is at about thirty, but the victim continues to plow and pick cotton throughout life. When sex-linked recessive it begins in the second decade; in the third decade such occupations as watch-making and book-keeping have to be abandoned, and the final stage is a crutch and a wheel chair. The recessive form begins before eight years of age and the victim is a hopeless cripple in the second decade. Lenz suggested that dominants are mild because lethal genes which are dominant will die out, but this does not apply to non-lethals. The views expressed earlier in this chapter, that the age of onset and the severity are determined by the behavior and strength of the gene, are also in accord with Allan's views. The "law of anticipation," if it exists, is evidently an independent phenomenon.

Related to anticipation is the condition described by Fleischer and others (see Chap. XXII) in which earlier generations of cataract at first senile, later progressing to earlier ages, are followed by a generation with myotonic dystrophy as well as cataract. Although this condition has been much studied, it requires fuller investigation before the relation between the cataract and myotonia can be fully understood. Both conditions occur in many pedigrees, the cataract appearing in earlier and myotonia in later generations. Goldschmidt (1938) has discussed this case, pointing out that Fleischer's pedigree was of a sedentary family of German peasants living in the same neighbourhood in good circumstances with a high birth-rate for eight generations. A total of about three thousand persons were finally included in the pedigrees, and half of them were alive when the work of Henke and Seeger (1927) was done. Senile cataract in the early generations is regarded as a condition of low penetrance and low expressivity of the single dominant gene. Later generations show an increase up to 50 per cent of visible heterozygotes and a simultaneous increase in the symptoms, which now include both cataract and muscular dystrophy, the former appearing at younger ages.

Goldschmidt draws an analogy between these conditions and the series of allelic mutations in Drosophila which begins with a nick in the wing and ends with no-wing. He found that vestigial wing, an intermediate in the series, is a case of hereditary dystrophy. In this series he concluded that lysis of the wing tissue proceeds to different stages in proportion to the time of onset, rate, and threshold, the lowest alleles producing a phenotypic effect in only a few offspring, but beyond a certain member of the series the penetrance and expressivity are complete. Vestigial wing is recessive since heterozygous individuals are normal; but a number of dominance-modifiers, which Goldschmidt[10] calls *dominigenes*, shift dominance toward the vestigial type. In low members of this allelic series there is only lysis of certain portions of the wings, but in the higher members there are additional abnormalities of venation, bristles, time of development and viability. Goldschmidt explains the case of cataract followed by dystrophy in later generations as the result of a similar accumulation of modifiers affecting penetrance and expressivity. The parallel, although incomplete, is of interest, but assuming that there are many dominigenes in the population, it is difficult to see why they should go on accumulating in a particular pedigree. Nevertheless, modifiers of dominance very probably play a part in human genetics, and they differ in some respects from Punnett's dominance inhibitors.

Some genes are asymmetrical in their effects. For instance, harelip and cleft palate are more frequent on the left than the right side, and the same applies to luxation of the femur, clubfoot and polydactyly. Certain other genes produce their effects more frequently on the right side of the body. In a usually bilaterally expressed gene, there must be a difference of penetrance on the two sides when the expression is unilateral.

Quite a number of human genes are now recognized as determining a single biochemical difference or the failure of a particular enzyme to be formed. In the case of phenylketonuria this is associated with serious mental defect, but some of the errors of metabolism are benign, producing no visible effect. In such cases probably very few chemical steps or none separate the gene from its final expression in the body. In the case of morphological defects it is much more difficult to understand how a difference which is basically chemical in every nucleus comes to express itself as a morphological change. In cases of chondrodystrophy, however, it is known that changes in certain enzymes are involved.

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[10] In a more detailed study of many wing-mutants in Drosophila, Waddington (1940) finds that Goldschmidt's assumption of lysis stopping at different points is incorrect. His analysis shows a much more complicated situation, sixteen different processes of wing development being involved in thirty-eight wing-mutations. The reply of Blanc (1942) brings no fresh evidence of lysis rather than retraction. Goldschmidt (*ibid.*, p. 122) states that scalloping effects can be produced or enhanced by dominant, recessive or modifying genes, inversions, triploidy, trisomy, temperature, X rays, etc.

Many *lethal factors* are known in domestic animals (Lerner, 1944) and in man. They were summarized by Eaton (1937), including seven lethal genes in man, but the number now known is considerably larger (see also Hanhart, 1942). Human lethals are a little difficult to define. They of course include all genes which bring the development to a fatal end before birth, but they should also include all genes, such as Morquio's disease, which produce death in childhood. Glioma retinae was formerly fatal in 100 per cent of cases in infants. Removal of the eye (one or both) now saves the child's life, but as the gene is dominant it should be the sacred duty of the surviving individual not to pass on his or her fatal defect to posterity. If this rule is not adhered to, the medical profession, in saving the life, will be made a partner to the reappearance of this fatal defect in the next generation. Since many single cases are fresh mutations, the increase of glioma can only be avoided if they are all prevented from reproduction.

Probably survival to reproductive age is the best criterion of a nonlethal gene, but cases in which the individual succumbs in childhood are frequently called *sublethal.* Strictly this term should be applied to those genes in which the mortality is less than 100 per cent. A gene such as that for Huntington's chorea, with onset in middle age and fatal termination later, should not be classed as lethal, because the individual has already reached or passed the reproductive age. In some pedigrees of hemophilia the gene is lethal or sublethal in the sense that affected males rarely or never live to the reproductive age. In other pedigrees, however, hemophilic males frequently reproduce and transmit their defective gene.

So far as known, most human lethal genes are recessive. A dominant lethal mutation necessarily ends with the same individual with which it began, and there is no present means of knowing how frequent such mutations are; but many severe congenital defects and monstrosities are probably of this nature. There are also probably human gametic lethals, as in plants and probably in animals, but these have not been investigated in man.

A lethal mutation in the Norway rat is described by Grüneberg

(1938), in which the gene, which is linked to pink-eye dilution, exerts pleiotropic effects. It produces an anomaly of the cartilage, which causes hyperplasia of the ribs and of the cartilage rings of the trachea. This in turn leads to emphysema of the lungs (air in the alveolar tissue) and dilatation of the bronchi. Death finally supervenes through one of several paths leading to suffocation, hemorrhage into the lungs or starvation. The original defect in certain cartilages leads in turn to several complex trains of events, any one of which ends fatally. As the remote effects are consequences of the original skeletal changes, this is mistakenly referred to as spurious pleiotropism, but in practice they may be regarded as pleiotropic effects. Grüneberg takes the view that no case of genuine pleiotropism, in which the same gene produces two or more independent effects, has yet been proven. Some of the hereditary syndromes (see Chap. XVIII) may be of this nature, but embryological as well as genetical evidence is required to prove it.

Recessive lethals are also common in wild populations of Drosophila and they doubtless occur in other wild animals. In wild *D. pseudoobscura*, for instance, from 15 to 30 per cent of the third chromosomes contain lethals or semi-lethals (Wright, Dobzhansky and Hovanitz, 1942), some of which are alleles. The number of loci in the third chromosome capable of lethal mutation is estimated at 285, and the mean mutation rate 1.077×10^{-5}. From this it would appear that lethals are probably more numerous in Drosophila than in man. Ives (1941) found a very high frequency of lethals in a wild population of *D. melanogaster*, associated with a high mutation rate — 1.8 per cent per generation in 437 tests.

The higher mortality of male embryos in man has been ascribed to sex-linked lethals, but this explanation is not universally accepted. It is well known (see Chap. XX) that the sex-ratio at birth is about 106, and Bunak takes the ratio at fertilization to be 115. This means a 9 per cent wastage of male embryos before birth, which may be due to sex-linked recessive lethals. Bedichek and Haldane (1938) point out that on this hypothesis, since two out of three X-chromosomes are in females, where such genes are protected from natural selection, the mutation rate in the X would be one lethal in 3 per cent of X-chromosomes per generation. If this very high rate applied to autosomes as well, the majority of human autosomes should carry at least one lethal. They also point out that if recessive lethals are common in human autosomes, the frequency of surviving recessives among the progeny of two heterozygous parents should be less when they are related than when they are unrelated, for in the former case some of them should contain the same recessive lethal gene as well as the same recessive non-lethal gene. Applying these ideas statistically to Pearson's data on albinism, the results were negative, i.e., there was no evidence of the presence of recessive lethals in the chromosome containing the gene for albinism. The number of known lethal genes in man becomes considerable if one includes all the recessive inherited conditions which are fatal in childhood.

Haldane (1938) has pointed out another relationship arising from the presence of lethals. Where a recessive gene has a lethal allele, the heterozygote of the two being abnormal, the frequency of consanguinity among the parents of abnormals should be reduced.

Two new lethals in the horse (Prawochenski, 1941) are (1) crippled legs with crooked phalanges, (2) absence of eye orbits. Both are regarded as polymeric recessives.

Cuénot showed in 1905 that homozygous yellow mice are lethal, and Kirkham in 1917 found the disintegrating embryos *in utero*. Robertson (1942) shows that these embryos develop normally through cleavage and blastocyst formation; but implantation fails to take place, the central cavity of the embryo collapses, and development ceases at about five days. When ovaries were transplanted from heterozygous yellow to agouti females, it was found that in the agouti uterus these yellow embryos develop further, forming about twice as many cells but dying after the beginning of implantation. The single gene difference between yellow and agouti must affect the uterine wall and so influence the development of the embryo.

The short-tailed mouse mutation is also lethal in the homozygous condition. These embryos die at the tenth day, the whole posterior end of the body being absent and the somites undifferentiated. Ephrussi (1935) made tissue cultures from the myoblasts, epithelial cells and fibroblasts of these embryos. They showed normal growth and dividing capacity, and the cartilage-forming mesenchyme had normal differentiating capacity, even when taken from the posterior end of the embryo. Since the individual cells have normal developmental capacities, it was concluded that the death of the lethal embryos was probably due exclusively to internal factors of interaction between tissues.

These results all have a direct bearing on the understanding of human lethals. Probably many miscarriages at different stages of development and many stillbirths are due to lethal factors.

Modern experimental work has shown that the relation between the developing organism and its environment is by no means a simple one. Different genes vary greatly in the degree of their response to particular environmental changes. One of the early cases of a gene which is peculiarly amenable to environmental changes was discovered by Morgan (1915). The Drosophila mutation, abnormal abdomen, has pigment bands on the abdomen which remain latent if the food is dry and only reach full expression when the larvae receive food having an abundance of water. Similarly, Hoge (1915) showed the influence of temperature on the gene that causes reduplication of legs. At normal temperatures few flies show the condition, but if the larvae are kept at a cold temperature the penetrance is complete. The phenotype of many Drosophila mutations is altered by exposing the young larvae to extreme heat or cold. In the mutant tetraptera, in which the halteres are changed to wings, the penetrance varies from 1 per cent at 17° C. to 35 per cent at 25° C. In the converse mutation, tetraltera, in which the pair of wings is changed into halteres, the penetrance ranged from less than 1 per cent at 29° C. to over 35 per cent at 14.4° C. The increased penetrance resulted from the slower rate of development at low temperatures, and not from the temperature itself. Villee (1943) has similarly shown that in the allelic series of aristopedia third chromosome mutations, in which an antenna is transformed into a tarsus with claws, heat treatment decreases the expression of the gene while cold produces various effects on different alleles, the most effective time of application being four days after larval development begins. The mutational replacement of an antenna (arista) by a leg can be developmentally explained by assuming that a leg evocator diffuses into the antennal disc before its development is sufficiently advanced to produce an antenna.[11]

The gene antennaless, on the second chromosome of Drosophila, prevents the formation of antennae under certain conditions. In hatching, the early flies show a high exhibition [12] of this recessive character (Gordon and Sang, 1941). The curve of exhibition frequently begins at a maximum, falls in four days to a minimum, then rises to near-maximum by the eighth day, after which it falls somewhat again. These rises and falls were shown to be due to changes in the culture medium, which depend upon changes in the microflora and metabolites in the food, thus involving changes of diet. This particular mutation is remarkably sensitive to small nutritional changes. The results were not due to selective mortality. The gene for antennaless acts between the third and fourth day of larval life. Temperature changes also have a striking effect on exhibition when the medium is sterile, while changing pH in the normal medium alters the exhibition frequency. The yeasts in the medium produce some substances which encourage and others which inhibit the exhibition of antennaless. These examples from Drosophila serve to indicate some of the ways in which certain human genes may be related to environmental conditions, but of course in mammalian development the temperature is normally held constant, so that other kinds of environmental changes or intra-uterine conditions must be invoked.

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[11] Another Drosophila mutation — podoptera — has recently been found (Goldschmidt, 1945) in which one wing is more or less changed to a leg. Rarely both wings are affected. It is allelic to tetraltera but has a still lower penetrance, only 0.25–3 per cent in homozygotes. This new case of a homoeotic mutation raises interesting questions regarding the origin of insect wings from primitive legs (parapodia of polychaetes).

[12] The term *exhibition* has been applied to the homozygous and penetrance to the heterozygous state.

It has been claimed that heterozygous female carriers of hemophilia can be detected by a difference in the clotting time of the blood, and there are many other cases in which it would be very important if carriers could be distinguished from homozygous normals. Probably, methods will ultimately be devised for determining such differences. The possibilities are indicated by an experiment of Hance (1928). When mice are exposed to X rays the hair falls out and in colored mice it may be replaced by white hair. Hance found that in mice homozygous for pigmentation the new hair contains pigment, whereas heterozygotes lose nearly all their color.

In all work in human genetics it has to be realized that the same conditions may be produced phenotypically or inherited genotypically in particular cases. Perhaps the most striking instance of this kind is that of a Nordic woman in whom a tumor of the pituitary produced all the Negro racial characters, including dark skin, frizzy hair, broad nose and thick lips (see Chap. XXIX).

Little is known regarding human mutation rates and the changes which they undergo. In characters such as the blood groups, which differ widely in racial frequencies, it is possible that changes in the mutation rate may be involved. One such change, in guinea pigs, has already been referred to. Several genes which affect mutation rates are now known in plants and animals. Demerec (1929) found both dominant and recessive genes affecting the mutation rate of unstable genes in Drosophila, and Sturtevant (1937) found a complex of genes controlling mutability. Dobzhansky (1941) has recently discussed the subject, pointing out that geographic strains of Drosophila species have different mutation rates. In some cases the position of the gene in the chromosomes may affect its mutation rate. Rhoades (1938) showed that the gene $\mathbf{a}_1$ in maize becomes highly unstable in the presence of a certain mutability modifier, and also (1941) that the mutation rate of unstable genes is depressed by high temperature.[13] Fabergé and Beale (1943) found a similar decrease in the mutability of an unstable gene in Portulaca through temperature disturbances. In *Drosophila pseudoobscura*, a gene, probably in chromosome II, produces a high general mutation rate in one strain (Mampell, 1943), the rate being thirty-four times the normal in heterozygous individuals and seventy times the normal in flies which are homozygous for the "mutator." There is thus evidence of genes affecting general mutability, others affecting the stability of particular genes, and environmental effects on mutation rates as well. Many cases of mutation in man are cited in this book, but little is yet known of their statistical frequency.

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[13] Rhoades (1945) has recently found that the highly stable gene **a** is in chromosome 3, while the gene **Dt** is in or near the terminal knob of chromosome 9

Different strains of *Drosophila melanogaster* are shown to have different mutation rates and the same may well be true of the human races. There is indeed evidence that the genes for certain inherited diseases are more frequent in some races than in others. Plough and Holthausen (1937) found a high mutation rate in a Florida strain of *D. melanogaster*, one particular stock having a mutation rate of three to six times the normal (*ca.* 35 mutants in 30,000 flies) while fourteen others simultaneously bred gave no mutations. Spencer (1935) found the mutations of *D. funebris* and *D. hydei* coming in waves, which may be accounted for by the inheritance of a mutability gene. Demerec (1937) measured the frequency of lethal mutations in the X-chromosome of fifteen stocks of *D. melanogaster.* He found a significantly higher mutation rate in three stocks, the highest of all being the Florida stock. In this strain he determined the presence of a recessive gene in chromosome II which increases the rate of visible mutations. He suggests that the action of this gene is to affect the gene environment in the cell so as to bring many genes to the threshold at which changes will occur. Tiniakov (1939) found a highly mutable stock of the same species near Moscow. In the progeny were 54 mutants among 8634 flies, whereas a normal stock produces about 5 mutants per 100,000 flies. Flies bred from other areas produced no mutants among 10,000 progeny. In a further study, Shapiro (1939) concludes that there is a continuous occurrence of mutations which increase the mutation rate, but that selection must eliminate them as they are obviously deleterious to the species.

Gene Distributions

It is not intended to enter into questions of population in this work, but there has been much recent study of gene distributions, cousin marriage and related problems, some of which may be briefly referred to here. The genetics of human populations is in some respects a distinct field from that of human individuals. In some respects it has advantages over the study of wild animal or plant populations, since the inheritance of any gene in individual families can be determined. It is important as far as possible to determine the genetic composition of particular populations, the nature of any external or internal factors which tend to change the equilibrium of population, and the way in which such influences act.

As a simple example of gene distribution in a wild animal population we may take the case of the black fox, as analyzed by Romashov and Ilyina (1942). The black fox differs from the ordinary red fox by a single gene, **B.** The genotype **BB** is black, the heterozygote **Bb** intermediate, the recessive red, **bb.** The frequency of the dominant gene **B** in northern Eurasia and North America varies in different areas from 0 to 8 per cent, and on an island off Kamchatka it reaches 25 per cent. The gene frequency for different areas was based on the numbers of skins of the three kinds collected in 1931. Using Hardy's formula, $p^2 + 2\,pq + q^2$, for the three types, the total results, omitting one aberrant area, were astoundingly close to expectation.

Totals found	12**BB** + 678**Bb** + 13655**bb**
Expectation	10.6**BB** + 681.4**Bb** + 13653**bb**

This shows that the mating between different types of foxes is random. It also proves that black and cross foxes are respectively the homozygous and heterozygous forms of the single gene **B.** In a study of the distribution of silver and cross foxes in Canada, Butler (1945) finds a gene **a** for silver, most abundant in Western Canada, another gene, **b,** increasing from west to east. There is also evidence of decreased fertility or survival of silver foxes.

In human populations, new genes arise by mutation from time to time and the same gene may arise repeatedly. The genic composition of a population can also change through selection, immigration or emigration, and through the occasional random extinction of rare genes. On the basis of certain assumptions, Haldane (1939a) derives formulae for the equilibrium between mutation rates and random extinction.

The expression for the genotypes in a population mating at random may also be written $p^2 : 2\,p(1 - p) : (1 - p)^2$. Any gene **A** in the population will then have the frequency p^2**AA** : $2\,p(1 - p)$**Aa** : $(1 - p)^2$**aa.** If 1 in 20,000 persons are albinos, then $p^2 = \frac{1}{20000}$, and $p = \frac{1}{141}$. The number of heterozygous carriers is $2\,p(1 - p) = \frac{1}{71}$. Hence 1 in about 71 will be a carrier.

Hogben (1931) showed that if a familial trait is determined by a single recessive gene, then $\dfrac{R}{\sum \dfrac{s.n_s}{1 - q^s}} = p$, where p is the probability that the offspring of two heterozygous parents will be recessive, R is the total number of recessives in families of at least one recessive, n_s is the number of observed s-membered fraternities containing at least one recessive, and $p + q = 1$. In general, the proportion of recessives in recorded families showing autosomal or sex-linked traits is significantly higher than one-quarter. This is because cases showing high familial incidence are recorded in medical journals more often than those with a low family incidence. It is therefore frequently necessary for statistical purposes to collect fresh data, including the family pedigree of every case in a long consecutive series. By such means it should be possible ultimately to obtain a good estimate of the frequency of many different genes in the population. Haldane (1932) devised a method for calculating the true proportion of recessives from small families, which involves more work than the Lenz-Hogben method but is more accurate.

Strandskov (1942) shows how the formula for determining the gene frequency from the phenotypic frequency depends on the manner of inheritance of the particular gene. Different systems of mating will affect the phenotypic frequency of a particular character, but not the frequency of its gene. Thus inbreeding will increase the frequency of the phenotypic appearance of a recessive gene, but if the homozygous phenotype of the gene is very deleterious it will actually become less frequent in later generations. Selection may thus operate differently on gene frequencies as a result of different systems of mating. Haldane and Moshinsky (1939) calculated the effects of cousin marriage on rare recessive genes which are completely or partially sex-linked.

Outbreeding tends to spread recessive genes through the population without bringing them to the surface. Inbreeding, on the other hand, as shown in the case of maize, pigs and many other organisms, brings deleterious genes to the surface where selection, natural or artificial, can act to prevent their reproduction. Inbreeding may therefore be racially advantageous in the long run, provided that any deleterious homozygotes which appear are prevented from reproduction. Strandskov makes the extraordinary statement that "basically, the populations (of different human races) are not different," thus flying in the face of all the facts of anthropology. Such a statement only serves to give a false perspective, for if it means that the different races have more genes in common than unlike genes, then the same statement would apply to man and the gorilla. Surely it is better to face the facts of racial difference than to try and camouflage them by such dicta, which are only misleading in their implications. Those who (unlike Strandskov) try to make out that all mankind are a single house-party, lacking only in a common feeling of fellowship, do an injustice to science, truth and eugenics, which has never contemplated universal mixture of races as a desirable future for mankind.

The question has often been raised, whether cousin marriage is a desirable thing. Formerly it was heavily penalized, and in A.D. 390 Theodosius the Great prohibited cousin marriage under severe penalties, including death. In an early study of cousin marriage in England, Elderton (1911) found no evidence that lessened fertility necessarily follows consanguineous marriage, some inconclusive evidence of higher child mortality in the offspring of cousin marriages, and definite evidence that the frequency of consanguineous marriages is greater among the parents of albinos, deaf-mutes and persons of unsound mind. She deduced that "there is a very large number of latent (recessive) defects in the community." Sjögren (1931) found that in the case of recessive juvenile amaurotic idiocy in Sweden the parents were first cousins in 15.3 per cent of cases, first cousins once removed in 3.4 per cent and second cousins in 6.8 per cent. Dahlberg (1939) showed a slow but steady decrease in the cousin marriage rate in Prussia and Bavaria between 1875 and 1933, while in France, where the rate is higher, the decrease between 1876 and 1919 was only from 1.03 to 0.97. Dahlberg shows higher consanguinity rates in the country than in towns. Bell (1940) finds from some 49,000 patients in hospitals of England and Wales that only 0.79 per cent were from consanguineous marriages, 0.61 per cent from first-cousin marriages, which is believed to be an underestimate for the country as a whole.

The danger that may attach to cousin marriage arises, not from inbreeding per se, but from the possibility that the family germplasm is carrying deleterious recessive genes. Each family can only be judged from its past history. Murphy (1924) described an immigrant family from Germany to Pennsylvania in 1731. The original immigrant left twenty-four children, one of whom settled in North Carolina in 1797. The families remained prolific and there were seven first-cousin marriages in four generations. The forty-one descendants show no physical abnormality and only one has slightly impaired mentality, but there is a high infant mortality, and the death-rate is definitely higher than in the general population.

Probably throughout human prehistory, when populations were small, the coefficient of inbreeding was high. How incest came to be taboo is a matter on which anthropologists do not agree. Haldane (1939b) points out that inbreeding has diminished within historical time, and particularly with increased modern urbanization and transport. He shows that relaxation of inbreeding in civilized countries must have resulted in rapid decrease in the frequency of lethal and sublethal recessive conditions, which will be followed by a slow increase in the frequency of these genes in the future population. In two thousand years or more they will rise to their old level, and he suggests that this is the reason why abnormal dominants are now much commoner than recessives in man. In a correction of this paper, Haldane (1940) found that the rapidity of the rise was overestimated. If several dominant genes produce diseases which are grouped together clinically, such as Friedreich's ataxia, and which differ in severity (graded according to the age of onset), then he shows that the frequency of affected individuals in the population will be close to an equilibrium value of $2\mu(1-f)$, where μ = the mutation rate and f = fitness. If there is one gene producing a mild disease with mutation rate μ_1 and fitness $f_1 = \frac{3}{4}$, and another gene producing the disease in severe form, with a mutation rate μ_2 and fitness $f_2 = \frac{1}{4}$; then he finds the frequencies at equilibrium will be $8\mu_1$ and $\frac{8}{3}\mu_2$, respectively. The mild type should then be three times as frequent, relative to its mutation rate, as the severe type. The same holds for recessive zygotes. When inbreeding is relaxed, the frequency of the severer recessive types of a disease should be increased relative to that of the milder dominant types. He believes that the later onset of dominant hereditary ataxia is due to the action of selection, but it seems more likely that it is a part of the difference between the dominant and recessive genes.

In another paper (1941), Haldane finds that in glaucoma, peroneal atrophy, Friedreich's ataxia, spastic ataxia and spastic paraplegia the age of onset is uniform in each pedigree but differs widely in different pedigrees, indicating that different genes are responsible. In optic atrophy and Huntington's chorea, on the other hand, the age of onset varies widely within a pedigree, so there is probably a single gene, with modifiers affecting the time of onset.

Statements have been made to the effect that heterosis or hybrid vigor is important in human racial crosses. This condition occurs in some crosses of animal and plant species, but not in others. As regards man, the idea has been vastly exaggerated. No one has yet produced any strictly genetical evidence of its occurrence in mankind, and theories based on its assumed effects are therefore fallacious.[14] There are two distinct effects ascribed to heterosis: (1) increase in size of the hybrid soma, (2) increase in fertility. Human beings are already so highly heterozygous that in any case race-crossing is unnecessary to produce a hybrid condition in man. Gowen (1945) has recently found that when races of Drosophila of different geographical origin are crossed, the hybrids show a marked increase in egg-laying as compared with the inbred strains. He concludes that this increased fertility is controlled by a number of genes distributed at random in the chromosomes. Notwithstanding much work on heterosis in plants and animals, and many theories (see Whaley, 1944), the ultimate causes of this scattered effect are still unknown. In certain cases in maize a single gene difference can produce marked heterosis.

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[14] An apparent exception is found in the Nilotic tribes of the Sudan. They are believed on good evidence (Seligman 1932) to be the result of a mixture of Hamite (Caucasian) and Negro stock; and their exceptional tallness is regarded as a result of this mixture, which may have begun as early as the pluvial age. However, no such effect is recorded in modern crosses between Caucasians and Negroes.

LITERATURE

Allan, W. 1937. Eugenic significance of retinitis pigmentosa. *Arch. of Ophthal.* 18:938–947.

———. 1938. Hereditary pattern determines clinical severity and eugenic indications. *Eugen. News.* 23:67–68.

Bampton, E. H. 1914. *Internat. Dent. Congr.* P. 167.

Bauer, J. 1945. *Constitution and Disease.* New York: Grune & Stratton. 2nd Edn. Pp. 247.

Bedichek, S. & Haldane, J. B. S. 1938. A search for autosomal recessive lethals in man. *Ann. of Eugen.* 8:245–254.

Bell, Julia. 1940. A determination of the consanguinity rate in the General Hospital population of England and Wales. *Ann. of Eugen.* 10:370–391.

Blanc, R. 1942. Observations on the production of wing scalloping in *Drosophila melanogaster. U. of Calif. Publ. Zool.* 49:1–10. Pls. 9.

Blunn, C. T. 1943. Characteristics and production of old-type Navajo sheep. *J. Hered.* 34:141–152. Figs. 5.

Burks, B. S. 1937. Studies of available data in connection with research projects in the field of human heredity. *Yearbook Carneg. Inst.* 36:312–319.

Butler, L. 1945. Distribution and genetics of the color phases of the red fox in Canada. *Genetics* 30:39–50.

Csik, L. & Mather, K. 1938. The sex incidence of certain hereditary traits in man. *Ann. of Eugen.* 8:126–145.

Dahlberg, G. 1939. On rare defects in human populations with particular regard to in-breeding and isolate effects. *Proc. Roy. Soc. Edinb.* 58:213–232.

Demerec, M. 1926. Genetic factors stimulating mutability of the miniature-gamma wing character in *Drosophila virilis. Proc. Nat. Acad. Sci.* 15:834–838.

———. 1937. Frequency of spontaneous mutations in certain stocks of *Drosophila melanogaster. Genetics* 22:469–478.

Dobzhansky, T. 1941. *Genetics and the Origin of Species.* 2nd Edn. Columbia Univ. Press. Pp. 446.

Dry, F. W. 1944. A possible gene duplication in New Zealand Romney sheep. *Nature* 154:552.

Dunn, L. C. 1941. Abnormal growth patterns: with special reference to genetically determined deviations in early development. *Third Growth Symposium.* Pp. 147–161.

Dunn, L. C. & Landauer, W. 1936. Further data on genetic modification of rumplessness in the fowl. *Journ. Genet.* 33:401–405.

Eaton, O. N. 1937. A summary of lethal characters in animals and man. *J. Hered.* 28:320–326.

Elderton, E. M. 1911. *On the Marriage of First Cousins.* London.
Ephrussi, B. 1935. The behavior in vitro of tissues from lethal embryos. *J. Exp. Zool.* 70:197–204.
Fabergé, A. C. & Beale, G. H. 1943. An unstable gene in Portulaca: mutation rate at different temperatures. *J. Genet.* 43:173–187.
Fortuyn, A. B. D. 1939. A mutation from agouti with recessive spotting to dominant spotting in *Mus musculus. Genetica* 21:92–96. Figs. 2.
Gates, R. R. 1915. Heredity and mutation as cell phenomena. *Am. J. Bot.* 2:519–528.
———. 1920. *Mutations and Evolution.* Cambridge Press. Pp. 110. Also in *New Phytol.* Vols. 19 & 20.
———. 1932. Nuclear structure. *J. Roy. Micro. Soc.* 52:1–19.
———. 1938. The species concept in the light of cytology and genetics. *Amer. Nat.* 72:340–349.
Goldschmidt, R. 1938. "Progressive heredity" and "anticipation." *J. Hered.* 29:140–142.
———. 1945. Podoptera, a homoeotic mutant of Drosophila and the origin of the insect wing. *Science* 101:389–390.
Gordon, C. & Sang, J. H. 1941. The relation between nutrition and exhibition of the gene antennaless (Drosophila melanogaster). *Proc. Roy. Soc.* 130B:151–184. Figs. 10.
Gowen, J. W. 1945. An analysis of the genic or cytoplasmic basis of heterosis. *Genetics* 30:7 (Abst.).
Grüneberg, H. 1938. An analysis of the "pleiotropic" effects of a new lethal mutation in the rat (*Mus norvegicus*). *Proc. Roy. Soc.* 125B:123–144. Pls. 4.
Haldane, J. B. S. 1932. A method for investigating recessive characters in man. *J. Genet.* 25:251–255.
———. 1938. A hitherto unexpected complication in the genetics of human recessives. *Ann. of Eugen.* 8:263–265.
———. 1939a. The equilibrium between mutation and random extinction. *Ann. of Eugen.* 9:400–405.
———. 1939b. The spread of harmful autosomal recessive genes in human populations. *Ann. of Eugen.* 9:232–237.
———. 1940. The conflict between selection and mutation of harmful recessive genes. *Ann. of Eugen.* 10:417–421.
———. 1941. The relative importance of principal and modifying genes in determining some human diseases. *J. Genet.* 41:149–157.
Haldane, J. B. S. & Moshinsky, Pearl. 1939. Inbreeding in Mendelian populations with special reference to human cousin marriage. *Ann. of Eugen.* 9:321–340.
Hance, R. T. 1928. Detection of heterozygotes with X-rays. *J. Hered.* 19:480–485. Figs. 3.
Hanhart, E. 1942. Über subletale Mutationen beim Menschen. *Arch. J. Klaus Stift.* 17:485–489.
Hogben, L. 1931. The genetic analysis of familial traits. I. Single gene substitutions. *J. Genet.* 25:97–112.
Hoge, M. A. 1915. The influence of temperature on the development of a Mendelian character. *J. Exp. Zool.* 18:241–297. Pls. 5.

Ibsen, H. L. & Cox, R. F. 1940. Inheritance of horns and scurs in sheep. *J. Hered.* 31:327–336. Figs. 10.

Ives, P. T. 1941. A high frequency of lethal mutations in a wild population of Drosophila. *Proc. Genet. Congr. Edinb.* P. 165.

Keeler, C. E. 1931. The independence of dominant spotting and recessive spotting ("piebald") in the house mouse. *Proc. Nat. Acad. Sci.* 17:101–102.

Lerner, I. M. 1944. Lethal and sublethal characters in farm animals. *J. Hered.* 35:219–224.

Levit, S. G. 1936. The problem of dominance in man. *J. Genet.* 33:411–434.

Macklin, M. T. 1932. The relation of the mode of inheritance to the severity of an inherited disease. *Human Biol.* 4:69–79.

Mampell, K. 1943. High mutation frequency in *Drosophila pseudoöbscura*, race B. *Proc. Nat. Acad. Sci.* 29:137–144.

Mather, K. 1938. Crossing-over. *Biol. Reviews* 13:252–292.

———. 1944. The genetical activity of heterochromatin. *Proc. Roy. Soc.* 132B:308–332.

Morgan, L. V. 1922. Non-criss-cross inheritance in *Drosophila melanogaster. Biol. Bull.* 42:267–274.

———. 1938. Origin of attached X-chromosomes in *Drosophila melanogaster* and the occurrence of non-disjunction of X's in the male. *Amer. Nat.* 72:434–446.

Morgan, T. H. 1915. The role of the environment in the realization of a sex-linked Mendelian character in Drosophila. *Amer. Nat.* 49:385–429.

Morrill, E. L. 1945. A new sex-linked defect in cattle. *J. Hered.* 36:81–82.

Murphy, D. P. 1924. Marriage of first cousins in direct line of descent through four generations. *J. Am. Med. Assn.* 83:29–30.

Neuhaus, M. J. 1936. Crossing-over between the X- and Y-chromosomes in the female of *Drosophila melanogaster. Zeits. f. Abst. u. Vererb.* 71:265–275. Figs. 4.

Pieraccini, A. 1901. Ulteriore contributo alle leggi che regolano la ereditarietà psicopatica. *Atta del II Congr. Freniatrico.* Reggio Emilia.

———. 1932. On the priority of the biological hereditary law of "anticipation." *Human Biol.* 4:554–557.

Plough, H. H. & Holthausen, C. F. 1937. A case of high mutation frequency without environmental change. *Amer. Nat.* 71:185–187.

Pontecorvo, G. 1943. Meiosis in the striped hamster. *Proc. Roy. Soc. Edinb.* 62B:32–42. Figs. 3.

Punnett, R. C. 1933. An ocular Mendelian puzzle. *Trans. Ophth. Soc. U. K.* 53:9–16.

Rhoades, M. M. 1938. Effect of the Dt gene on the mutability of the a_1 allele in maize. *Genetics* 23:377–397.

———. 1941. The genetic control of mutability in maize. *Symp. Quant. Biol.* 9:138–144.

———. 1945. On the genetic control of mutability in maize. *Proc. Nat. Acad. Sci.* 31:91–95.

Robertson, G. G. 1942. An analysis of the development of homozygous yellow mouse embryos. *J. Exp. Zool.* 89:197–227. Pls. 2.

Romashov, D. D. & Ilyina, E. D. 1942. Analysis of fox populations after Hardy's formula. *Doklady Acad. Sci. U.R.S.S.* 37:193–196.

Seligman, C. G. & Seligman, B. Z. 1932. *Pagan Tribes of the Nilotic Sudan.* London. Pp. 565.

Shapiro, N. I. 1939. Rate of spontaneous mutation-process in *Drosophila melanogaster. C. R. (Doklady) Acad. Sci. U.R.S.S.* 24:580–583.

Snyder, L. H. 1942. The mutant gene in man. *Am. Nat.* 76:129–143.

Spencer, W. P. 1935. The non-random nature of visible mutations in Drosophila. *Amer. Nat.* 69:223–238.

Stern, C. 1943. Genic action as studied by means of the effects of different doses and combinations of alleles. *Genetics* 28:441–475.

Stern, C. & Heidenthal, G. 1944. Materials for the study of the position effect of normal and mutant genes. *Proc. Nat. Acad. Sci.* 30:197–205.

Stern, C. & Schaeffer, E. W. 1943. On wild-type iso-alleles in *Drosophila melanogaster. Proc. Nat. Acad. Sci.* 29:361–367.

———. 1943a. On primary attributes of alleles in *Drosophila melanogaster. Proc. Nat. Acad. Sci.* 29:351–361.

Strandskov, H. H. 1942. The genetics of human populations. *Am. Nat.* 76:156–164.

Sturtevant, A. H. & Beadle, G. W. 1939. *An Introduction to Genetics.* Saunders. Pp. 391.

Sturtevant, A. H. & Tan, C. C. 1937. The comparative genetics of *Drosophila pseudoöbscura* and *D. melanogaster. J. Genet.* 34:415–432.

Tinikov, G. G. 1939. Highly mutable stock from a wild population of *Drosophila melanogaster. C. R. (Doklady) Acad. Sci. U.R.S.S.* 22:609–612.

Villee, C. A. 1943. Phenogenetic studies on the homoeotic mutants of *Drosophila melanogaster.* I. The effects of temperature on the expression of aristapedia. *J. Exp. Zool.* 93:75–98.

Waardenburg, P. J. 1932. Das menschliche Auge und seine Erbanlagen. *Bibliogr. Genet.* Vol. 7. Pp. 631.

Waddington, C. H. 1939. *An Introduction to Modern Genetics.* Macmillan. Pp. 441.

———. 1940. The genetic control of wing development in Drosophila. *J. Genet.* 41:75–139. Pls. 4, figs. 15.

Warwick, B. L. & Dunkle, P. B. 1939. Inheritance of horns in sheep. *J. Hered.* 30:325–329. Figs. 8.

Whaley, W. G. 1944. Heterosis. *Bot. Rev.* 10:461–498.

Wilson, E. B. The sex chromosomes. *Arch. f. mikr. Anat.* 77:249–271. Figs. 5.

Wright, Sewall. 1934. Genetics of abnormal growth in the guinea pig. *Cold Spring Harbor Symposia in Quant. Biol.* 2:137–147.

Wright, S., Dobzhansky, Th. & Hovanitz, W. 1942. The allelism of lethals in the third chromosome of *Drosophila pseudoöbscura. Genetics* 27:363–394.

Chapter III

HUMAN CYTOLOGY

IT IS now recognized that all the races of man probably have 24 pairs of chromosomes. This means that the human genes fall into 24 linkage groups. Because of the relatively large number, it is difficult to discover cases of genetic linkage in man. Apart from those linked with sex and carried in the XY pair of chromosomes, relatively few cases of genetic linkage in man have been proven (see Chap. IV). The cytological technique for the study of chromosomes in mammals and man has reached a point where accurate counts are being made even of large numbers. The earlier counts, before about 1920, were frequently erroneous, as mammal chromosomes are particularly soft and difficult to deal with. Table 3 gives a partial list of what may be regarded as accurate counts in mammals, except the first two. McClung (1939) has compiled a recent list of all chromosome counts in animals.

It will be seen that in Marsupials the most common number is 22, although 12 or 14 also occur in a number of species. The placental mammals practically all have higher numbers. In the Edentata and the Ungulata so far as known the usual number is 60, although the pigs and their relatives have about half that number. The Carnivora range from 34 in the fox to 78 in domestic dogs, but we may surmise that the latter number represents an increase as a result of crossing in the ancestry of the dog. Among rodents the numbers range widely from 40 to 42 in mice and rats to 62 in certain squirrels and even to 84. The last three groups, so far as now known, are represented almost entirely by 48 chromosomes, although a Cebus monkey has 54. It appears probable that the number 48 is of ancient origin and as characteristic of primates as 60 is of ungulates. Haase-Bessell (1936) suggested that the chromosome number in man was doubled during the Ice Age, but it seems more likely that the doubling occurred much earlier, at least as far back as the origin of the primates.

Biesele, Poyner and Painter (1942) find four nucleoli in normal human tissues, which supports my view that 48 is a tetraploid number.

It was formerly contended that doubling of the chromosomes could not occur in bisexual organisms with differentiated sex chromosomes because the XY mechanism would be upset. It turns out, however, that in various dioecious plants, such as *Melandrium* and *Carica papaya*, where sex chromosomes are present, experimentally produced tetraploids are male or female, with only occasional intersexes (see Gates, 1942b). The species of Salix are normally dioecious, yet they are known frequently to produce catkins showing various intersexual conditions (see Smith, 1940). Wilkinson (1941) has shown that *S. alba* and *S. fragilis* are both allotetraploids [1] with 76 chromosomes, including two pairs of chromosomes with satellites (one pair of satellites has been lost in *S. alba* var. *coerulea*, the cricket bat willow) yet they normally retain their bisexual character. There remains no reason why animals should not have done the same after doubling their chromosomes. Intersexes in dioecious plants are due to the interplay of external and internal determiners, frequently accentuated by hybridization. In animals and man they appear to be more largely determined by internal germinal and endocrine conditions (see Chap. XX). The relatively frequent intersexes in man may arise in part from the tetraploid condition of his chromosomes.

It will be noticed (Table 3) that an unequal pair (XY) of sex chromosomes is present in nearly all mammals accurately studied. There was a lengthy controversy as to whether man had a Y-chromosome, but the cytological evidence of its presence is strong, especially as Winiwarter and his school, who found no Y in man, found none in other mammals where many investigators have shown its presence. Winiwarter (1934) found 35 chromosomes, including an X, in a male Belgian cat, but he accepts the presence of 38 with an XY pair in preparations made from a male cat in Japan, and Koller (1941) has since found 38 in a Scottish cat. If the chromosomes of the domestic cat vary to this extent in different parts of the world, the same may well be true of man.

Winiwarter and Oguma (1926) studied spermatogenesis in six white and one yellow man, finding that all had an XO sex chromosome mechanism. Painter (1923), on the other hand, has investigated both whites and blacks, finding an XY pair in both races. Evans and Swezy (1929) obtained similar results with Mexicans (partly Indian) and whites. Oguma (1937), in a study of Manchurians and Japanese, contends that the X is made up of three segments, the terminal segment being mistaken for the Y; but apparently this is the XY pair attached endwise, as described by many investigators. The significant fact that

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[1] This means a new form produced by doubling of the chromosomes in a (usually sterile) interspecific hybrid

TABLE 3

CHROMOSOMES IN MAMMALS AND MAN

Monotremata	2 n	*Sex Chromosomes*	*Author*
Echidna	8–12	—	Benda, 1906 (from McClung, 1939)
Ornithorhynchus	8–12	—	Benda, 1906 (from McClung, 1939)
Marsupialia			
Dasyurus maculatus	14	XY	Greenwood, 1923
Sarcophilus ursinus	14	XY	Greenwood, 1923
Didelphys virginiana	22	—	Painter, 1922
D. aurita	22	XY	Dreyfus & Campos, 1939
D. paraguayensis	22	XY	Saez, 1931
Isoodon obesulus	14	XY	Drummond, 1933
Pseudochirus peregrinus	20	—	Altmann & Ellery, 1925
Petauroides volans	22	XY	Agar, 1923
Phascolarctus cinereus	16	—	Greenwood, 1923
Petaurus breviceps	22	XY	Drummond, 1933
Trichosurus vulpecula	20	—	Altmann & Ellery, 1925
Bettongia lesueuri	22	XY	Drummond, 1933
B. penicillata	28	XY	Drummond, 1933
Potorous tridactylius	12	—	Altmann & Ellery, 1925
Macropus ualabatus	12	XY	Agar, 1923
M. giganteus	22	—	Binder, 1927
Lutreolina crassicaudata	22	XY	Saez, 1938
Setonyx brachyurus	22	XY	Drummond, 1933
Phascolomys mitchelli	14	—	Altmann & Ellery, 1925
Edentata			
Tatusia novemcinctum (armadillo)	60	XY(?)	Painter, 1925
Ungulata			
Poephagus grunniens (yak)	60	XY	Zuitin, 1938
Bos taurus (cattle)	60	XY	Krallinger, 1927, 1931
Capra hircus (goat)	60	XY	See Oguma & Kakino, 1932
Equus caballus (horse)	60	XY	Painter, 1924
Equus asinus (donkey)	60	—	See McClung, 1939
Ovis aries (sheep)	60	—	Bruce, 1935
Ovis Poli	60	—	Zuitin, 1935
Ovis steatopyga	60	—	Zuitin, 1935
Leicester sheep	54	XY	Ahmed, 1940*
Rambouillet sheep	54	XY	Berry, 1941*
Sus scrofa (pig)	38		Krallinger, 1931†
Sus scrofa	40		Hance, 1917
Large white Yorkshire	38	—	Bryden, 1933
Pecari tajacu (peccary)	30	—	Krallinger, 1936
Carnivora			
Felis domestica			
(cat) In Belgium	♂35	XO	de Winiwarter, 1934
In Japan	♂38	XY	de Winiwarter, 1934
In Scotland	♂38	XY	Koller, 1941
Nyctereutes viverrinus	42	XY	Minouchi, 1929

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* These authors find 54 chromosomes in the sheep, including a heteromorphic XY pair, and three large V-shaped pairs which it is reasonable to assume have been formed by end-to-end fusion of 6 rod pairs, thus reducing the chromosome number from 60 to 54.

† Krallinger suggests that the counts of 38 and 40 obtained in domestic pigs result from the fact that they are derived from crosses between *S. scrofa* and *S. vittatus.*

TABLE 3 — *Continued*

Monotremata	*2 n*	*Sex Chromosomes*	*Author*
Canis familiaris (dog)	78	XY	Minouchi, 1928b
(dog) 3 breeds	78	XY	Ahmed, 1941
Vulpes fulvus (fox)	42	XY	Wodsedalek, 1931
Vulpes fulvus (fox)	32	XY	Bishop, 1942
V. lagopus (fox)	52	——	Andres, 1938
V. vulpes (fox)	34	XY	Wipf and Shackelford, 1942
Rodentia			
Cavia cobaya (guinea-pig)	60–64	XY	League, 1928
Citellus decemlineatus	50–54	XY	See Oguma & Kakino, 1932
Cricetus auratus	38	XY	Koller, 1938
	44	XY	Husted et al., 1945
Dipodomys merriami	86?	XY	Cross, 1931
Geomys breviceps	84?	XY	Cross, 1931
Glaucomys volans	52	XY	Cross, 1931
Lepus cuniculus (rabbit)	44	XY	Painter, 1926
Microtus townsendii	50	XY	Cross, 1931
Rattus norvegicus albus × *R. norvegicus*	42, 62	XY?	Swezy, 1927
Rattus novegicus albus	42	XY	Minouchi, 1928a
Rat	42	——	Bryden, 1932
Mus musculus	40	XY	Cox, 1926
Mus musculus	40	XY	Cutright, 1931
Rattus rattus alexandrinus	40	XY	Cross, 1931
Rattus coxinga	42	——	See McClung, 1939
Mus wagneri albula	40	XY	Minouchi, 1928c
Neotoma floridanus attwateri	52	XY	Cross, 1931
Perognathus fallax fallax	44	XY	Cross, 1931
Peromyscus spp.	48	XY	Cross, 1931
Peromyscus maniculatus hollesteri	52	XY	Cross, 1931
Peromyscus eremicus eremicus	*ca.*60	——	See McClung, 1939
Sciurus carolinensis carolinensis	48	XY	Cross, 1931
Sciurus leucotus (gray squirrel)	28	XY	Koller, 1936
Sciurus niger	62	XY	Cross, 1931
Sigmodon hispidus texianus	54	XY	Cross, 1931
Insectivora			
Crocidua (*Pachyura*) *murina*	40	XY	Tateishi, 1937
Mogera insularis	16	XY	Tateishi, 1937
Erinaceus europaeus	48		Painter, 1925
Chiroptera			
Nyctinomus mexicanus (house bat)	48	XY	Painter, 1925
Primates			
Rhesus macacus	48	XY	Painter, 1924
Brown Cebus monkey	54	XY	Painter, 1924
Chimpanzee	♂ *ca.*48	——	Yeager, Painter & Yerkes, 1940
Man			
White	47, 48	XO	Winiwarter, 1912
White	♂48	XY	Painter, 1923
Negro	48	XY	Painter, 1923
Japanese	47, 48	XO	Oguma & Kihara, 1923
Japanese	48	XY	Minouchi & Ohta, 1934
Negro, Mexican(?)	♂48	XY	Evans & Swezy, 1929
White	♀48	——	Swezy & Evans, 1930
White	♂48	——	Kemp, 1930
White	♂48	XY	Koller, 1937

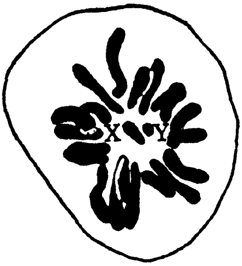

Fig. 14. Human spermatogonial cell showing the X- and Y-chromosomes. (After Painter)

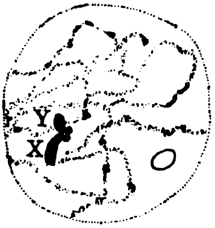

Fig. 15. Pachytene stage of spermatogenesis, showing X and Y. (After Koller)

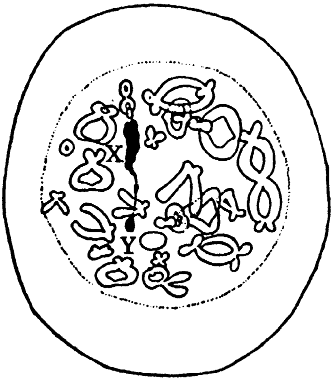

Fig. 16. Diplotene stage showing X and Y attached by their terminal satellites. (After Koller)

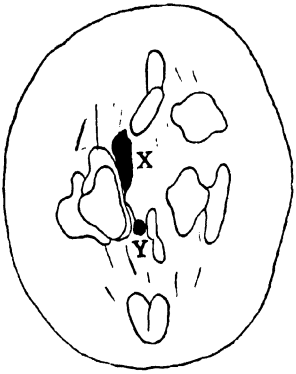

Fig. 17. First meiotic division, showing the X and Y separating. (After Painter)

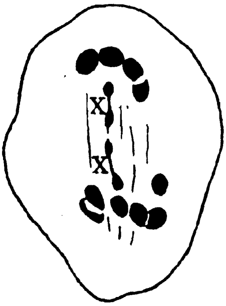

Fig. 18. Second meiotic division, showing the X dividing. (After Painter)

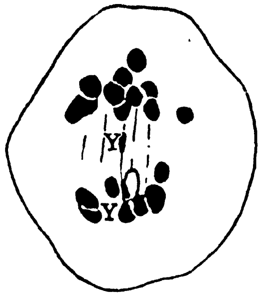

Fig. 19. Second meiotic division, showing the Y dividing. (After Painter)

in most dioecious plants and in many animals the XY pair is also the satellite (or nucleolus-producing) pair has been pointed out elsewhere (Gates, 1939, 1942a). The failure to find a Y is, therefore, rather a matter of interpretation than an actual difference, although it is possible that certain men may lack a Y, as it frequently lags in anaphase and is therefore in danger of being left out of the daughter nuclei. Matthey (1938) finds an XY pair in all the rodents and incidentally refers to species in which $2n = 32, 36, 46, 48, 50$ and 56 have been counted.

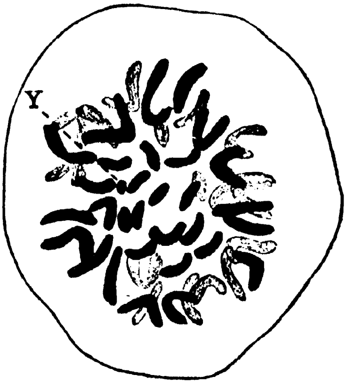

Fig. 20. Dividing somatic cell with 48 chromosomes, including the Y. (After Evans and Swezy)

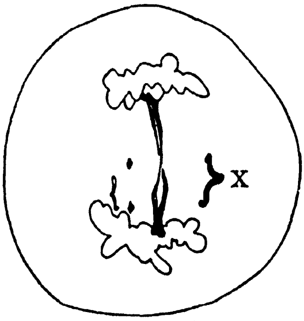

Fig. 21. First meiotic anaphase, showing the result of crossing-over in inversions. (After Koller)

The technical difficulties of investigating human chromosomes are great, but they are being overcome. A few selected figures will show the conditions. Figure 14 shows a spermatogonial cell in which the larger X and smaller Y can be recognized. Figure 15 shows the condensed pair of XY chromosomes in the pachytene stage of spermatogenesis, when the threads of the other chromosomes are already paired. It will be seen that the X and Y each appear to have a satellite, and probably each produces a nucleolus at this point at an earlier stage. Figure 16 represents the later diplotene stage in which the XY pair are attached by their terminal satellites. Figure 17 shows a side view of the spindle, with the X and Y separating in advance of the other bivalents. In the second meiotic division, all the chromosomes, including the X and Y, divide, as shown in Figs. 18 and 19. The X is seen dividing in Fig. 18 and the Y in Fig. 19. Half the sperm thus receive an X and half receive a Y. Figure 20 shows a somatic cell (mesenchyme) dividing, with 48 chromosomes, including the small Y. King and Beams (1936), in a study of spermatogenesis in six men fifteen to twenty-six years old, found 24 as the reduced number and that an XY pair was present among the 24 tetrads of the first spermatocyte.

The chromosomes of three men were carefully investigated by Koller (1937). One of them, who was descended in the second generation from a cross between Scotch and French, shows a peculiarity in spermatogenesis. In the first meiotic division the X and Y frequently divide equationally (Fig. 21). The other chromosomes have separated, except one pair which form a double bridge with fragments. It has been shown in many plants and animals that such conditions arise when the organism is heterozygous for an inversion in a segment of a chromosome. This opens up a large field for the study of chromosome inversions in human hybrids throughout the world. They are most likely to be found in crosses between races that have long been separated, and their occurrence should serve not only to identify certain chromosomes but also, as in Drosophila species, they may give some idea of the relative times when these inversions and other rearrangements of the chromatin took place. In this way, cytological evidence of human racial history may be obtained; but with the large number of chromosomes involved, it cannot be expected that the same chromosome will undergo many successive changes in such a way that they can be chronologically related to each other.

Koller finds that the X in man is 4–5 μ in length, the Y 1.5 μ, the X having a subterminal spindle fibre attachment. It also appears to have a terminal satellite. He finds that about two-thirds of the length of the X consists of the non-pairing segment, whereas the non-pairing segment of the Y is very small. The pairing segments of the two chromosomes should of course normally be of equal length. Koller concludes that (as in some mammals, e.g., the golden hamster) there are two kinds of sex bivalent, an asymmetrical in which the X and Y will separate in the first division, and a symmetrical in which they divide equationally in the first division and separate in the second. The symmetrical type is estimated to occur in 10 per cent of cases. Occasionally the X and Y fail altogether to pair. Crossing-over will take place between the pairing segments of the X and Y when they pair. The paired segments are believed to be over fifty cross-over units in length. Genes in this region will show incomplete sex linkage, while those in the unpaired segment of the X will show complete sex linkage and those in the unpaired portion of the Y will show male-to-male inheritance. The spindle attachment is believed to be in the pairing segment (see Fig. 23, p. 81). These conditions are essentially similar to those found in the Norway rat (Koller and Darlington, 1934).

Russian workers have made important contributions to human cytology. Chruščov (1934, 1935) appears to have been the first to make cultures of human leukocytes for the study of the chromosomes. Varela and Saez (1934) removed bone marrow cells from the manubrium of the sternum or from the tibia under local anesthesia and cultured them for chromosome studies. It is to be hoped that such methods will be followed up, as they should make possible the determination of the chromosome number and morphology in any individual. Kemp (1929) made careful earlier counts of 48 from the spleen and liver of a human embryo and from fibroblasts of various organs in tissue culture. In certain cases he found only 47 chromosomes. Schachow (1926) found 48 in the decidua of embryos, 24 in cells of the chorion (84 counts) with occasionally 23 or even only 8. Probably the counts of 24 resulted from fusion of pairs. This is frequently a result of the treatment, but it might be a natural somatic synapsis. Shiwago and Andres (1932) found 24 pairs in spermatogenesis, including an XY pair, the X being about three times the length of the Y.

Andres (1933) studied polyploid conditions in spermatogonia. He found cells having 2, 3, 4, occasionally 5 and once 7 nuclei. The three nuclei in one spermatogonial cell contained respectively *ca.* 45, 39 and 36 = 120 chromosomes. A cell was also observed with three nuclei and at least 60 bivalents, but no other irregularity. In addition to multinucleate cells there were spermatogonial nuclei with a single giant group of chromosomes, *ca.* 150–200. Six late prophase groups in giant spermatogonia were analyzed. In four the count was 96, one 97, one 98 (hence tetraploid). In two spermatocytes 48 bivalent chromosomes were counted. The second reduction division was seen in two such spermatocytes, and two giant spermatids were observed. Hence it is clear that typical giant spermatids and sperms with 48 chromosomes are formed, although the multinucleate spermatogonia probably produce several-headed sperms, such as have been observed. The existence of diploid sperm makes possible the occurrence, as a rarity, of 3 *n* individuals with 72 chromosomes. Their sex chromosomes could be (1) XXX, (2) XXY or (3) XYY. (1) would be a triploid female, (2) perhaps an intersex, and (3) might be a hypermale.

In a morphological analysis of human chromosomes, Andres and Navashin (1935) used the ovaries of four to five months embryos, the testes of two Russians, scrapes from a uterus, the amnion of an eight to nine weeks foetus, tissue cultures of embryonic lung and embryonic mesenchyme, a culture from the skin of a man sixty years old who had Karposi's sarcoma, and the testis of a Japanese. From a study of thirty-four orthoploid sets they distinguished the ten largest pairs of chromosomes, all differing in size and in the position of the spindle fibre attachment (i.e., in shape). Number 9 was a rod-shaped chromosome with a satellite, evidently the X. The 10th also was a rod with subterminal spindle attachment. Measurements showed that chromosomes Nos. 1, 2 and 3 were considerably longer in Japanese than in Russians, while Nos. 4, 6 and 8 coincided in length. Painter (1923, 1924) found that in the Negro the largest chromosome was J-shaped (No. 2) and Oguma (1930) compared the chromosomes of Japanese and

Belgians. There is thus already evidence of differentiation in the karyotypes of different human races, as well as inversion in certain chromosome segments of a population

In an extended study of the somatic chromosome complex in human embryos, Andres and Jiv (1936) found many variations from the diploid number, 48. About 49 per cent of cells were orthoploid. In the rest the numbers ranged from 32 to 73 chromosomes, but no essential differences were found between the extra-embryonic and embryonic tissues. The cells of epithelium, brain, mesenchyme of the skin, lung and intestine, epithelium of lung and intestine, showed in the main the same karyological picture. Unfortunately, no studies were made of such organs as liver, kidney and thyroid. The variations were attributed mainly to non-disjunction of one or several pairs, but fragmentation, association and elimination probably played some part. Among 900 cells in which counts were made, 6.4 per cen showed departure from a normal spindle.

In a study of eleven foetal ovaries of age two and one-half to eight months, Andres and Vögel (1935, 1936) found that the egg nucleus remains in the zygotene (paired thread) condition until the maturity of the follicle. Graafian follicles were sometimes found containing 2 or 4 ova. There were 48 chromosomes, including XX and the 10 recognizable pairs. A few oögonia showed polycentric mitoses, and lagging chromosomes which were eliminated, leading to irregular numbers. In one oögonium 87 chromosomes were counted and it is evident that tetraploid germ cells may be formed during oögenesis, just as they are in spermatogenesis. That being the case, individuals with 3 *n* and 4 *n* chromosomes may be expected to arise occasionally. The probability of their occurrence is increased by the fact (Fankhauser, 1941) that 3 *n* and 4 *n* salamanders can be produced. They are not gigantic, having larger but fewer cells. Fankhauser (1940) also found a pentaploid newt larva with larger cells and nuclei. He has since (1945) compared the effects of polyploidy (and haploidy) on the size of nuclei, cells and body in Amphibia, as well as the effect on rate of development, physiology and other features.

The occurrence of polyovular Graafian follicles in man and various mammals is recorded by Kennedy (1924). He concludes that it is not extremely rare, having been recorded in the human ovary by five different authors. He published photographs of polyovular and biovular follicles in the dog, cat and rabbit, and they have since been recorded in various other mammals. Such occurrences in woman serve as the basis for the production of some twins and multiple births (see Chap. XXI). A case of twin pregnancy with a single corpus luteum is described by Wieman and Weichert (1936) and is believed to have been from two egg cells in a single follicle. A remarkable case on record is that of a negress of eighteen (Arnold, 1912) whose ovaries (both normal) were removed. Practically every follicle in both ovaries contained more than one ovum. There were 88 large follicles, 35 contained two oöcytes, 10 contained three, 20 contained four, 1 contained eleven and 1 contained thirteen oöcytes. Here was a potential mother of multiple births. Such a condition must have been germinally determined. Presumably two egg nuclei from one follicle after meiosis and the formation of polar bodies, would be no more alike genetically than egg cells from separate follicles.

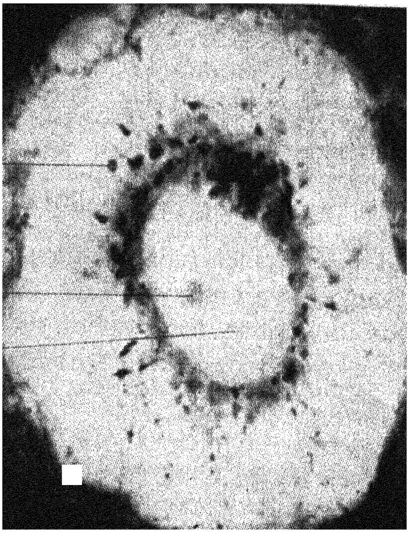

Fig. 22a. Photograph of human oöcyte. (After Aykroyd)

Aykroyd (1938) concludes that maturation begins in the follicle but is not completed before ovulation. Figure *22a* is a photograph of an oöcyte, showing Golgi bodies around the nucleus. By use of the ultracentrifuge, she finds in the cytoplasm of human oöcytes cholesterol (containing fat), Golgi bodies and mitochondria. E. Allen *et al.* (1930) found tubal ova in the second maturation division with adherent polar bodies. In a case of twin eggs, one in each tube, the diameter, including the zona pellucida, was 131–134 μ. Hamilton (1944) shows that the second maturation spindle (Fig. *22b*) persists until after ovulation, but the number of chromosomes present was not determined.

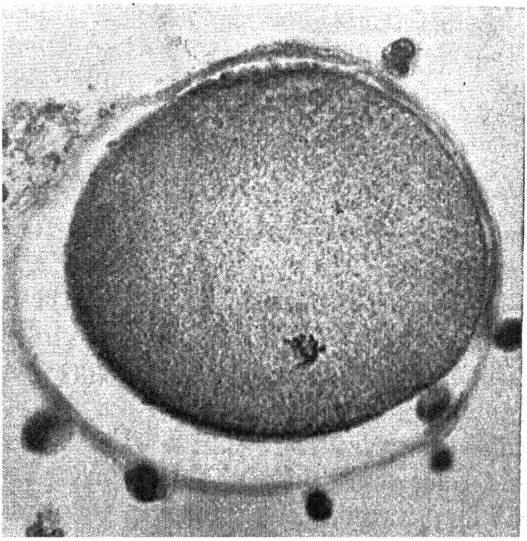

Fig. 22b. Photograph of human oöcyte. (After Hamilton)

That the possible peculiarities in human reproduction are not yet exhausted is shown by the work of Nicholas and Hall (1942) on rat embryos. They isolated the two blastomeres of a fertilized dividing egg in the two-cell stage and obtained development of each *in utero* up to stages of gastrulation. In another experiment two fertilized eggs were caused to fuse. This fusion product later produced *in utero* a giant individual, somewhat abnormal but with nuclei of normal size. This type of giant has also been found in Ascaris and in Nemertean worm embryos.

Tissue Polyploidy and Polyteny

That polyploidy of the nuclei in certain tissues is a constant feature of ontogeny in many insects is now well known. Frolova (1929) found that in Diptera the cells of the tracheae, the fat bodies, Malpighian tubules and rectal gland were regularly 4 n or 8 n, and that many organs of the larvae were polyploid. In sawflies, Sanderson (1933) found tetraploid hypodermal cells and large fat cells and oenocytes which were 16-ploid. Berger (1938, 1941) and earlier workers showed that in the mosquito, *Culex pipiens*, where $2n = 6$, the epithelial cells of the pupal ileum undergo polyploidy during development to as many as 96 chromosomes (32 n). This multiplication of chromosomes during the larval resting period can take place in the resting nuclei and is believed to be followed by a series of somatic reduction divisions until the diploid condition is again reached.

A full review of somatic polyploidy in plants is given by Srinath (1939). Tetraploid sectors of a root are of frequent occurrence in some plants and occasional tetraploid cells or groups of cells have been found in other tissues. Binucleate and 4 n pollen mother cells have also been described a number of times. In Calceolaria, Srinath found not only somatic doubling but also a hexaploid cell in a tetraploid root and triploid cells in the root of a tetraploid species, thus showing both gain and loss in sets of chromosomes.

Freerksen (1933) made a study of nuclear volumes in the different organs of guinea pigs and rabbits and their embryos. They were found to fall into classes with volumes 1 : 2 : 4 : 8 · · · 256, i.e., nine size classes, K1 nuclei having a volume of *ca.* 1 μ^3 when fixed in Zenker fluid. Erythroblasts of rabbits fell in classes K1, K2, K3. K5 was found in most organs except those of the central nervous system. K6 is present in liver, kidney, thyroid, cornea, etc.; K7 in fibroblasts and other cells; K8 in germ cells, the cerebrum, Purkinje cells, etc.; K9 in the cerebrum and Gasserian ganglion (guinea pig). The volume classes of rabbit and guinea pig agree, except that K1 is not found in the latter. The growth and division of nuclei thus follow volumetric laws, some nuclei remaining the same size as in the fertilized egg while others become either larger or smaller. The relation of these nuclear sizes to polyploid or polytene (multiple strands in the chromosomes) conditions remains to be determined. Nuclear size may be merely correlated with the amount of nucleic acid, but the larger sizes may indicate polytene conditions.

Similar measurements of nuclei made by G. Hertwig (1935) in Drosophila indicate that the same volumetric relations hold for insects as for mammals, the size classes falling into the same series. The giant "salivary" gland cells have nuclei 256 times as large as the smallest tissue cells. It has been assumed that some giant salivary chromosomes consist of 8 parallel strands, but if the volume relationships of the nuclei are an indication of the degree of polyteny (internal division into strands) of the chromosomes, the number of strands should be 256 since the chromosome number is unchanged. The evidence indicates that in some animal tissues (unlike plants) the nuclei can increase in size by undergoing polyteny instead of polyploidy (multiplication of chromosome number). Painter (1940) has discussed some of these relations, but in most animal tissues the relation between the duplication of strands and the division of chromosomes, or the degree to which one can replace the other, remains obscure.

Jacobj (1935) made an elaborate study of nuclear volumes in human tissues. In the liver he found nuclear volumes of 1 : 2 : 4 or 128 : 256 : 512 μ^3 (K1, K2, K4), while in the newborn they were nearly all K1 (a few K2), indicating a progressive later increase in size by definite steps which he ascribed to "amitosis." In mouse and rat livers he had previously found four sizes in the same series — K1, K2, K4, K8. Human thyroid showed K1, K2 and a few K4, while spinal ganglion cells were K8, K16, K32. Pancreas, parotid and lachrymal glands were K1, while the smallest nuclei were in erythroblasts (normoblasts) K$\frac{1}{8}$ and microlymphocytes K$\frac{1}{4}$. Epithelial cells (thymus), rod cells of the retina and spermatids contained nuclei whose size was K$\frac{1}{2}$. Jacobj suggests that increase of the chromosome size may take place, to account for the geometric increase in nuclear volumes. If polyploidy were involved and K1 nuclei had 48 chromosomes, K8 nuclei should have 384. He produces no cytological evidence of any change in chromosome number. Collin and Florentin (1930) confirmed Jacobj's earlier work. Using the infraorbital gland of the white rat, they found nuclear volumes in the ratio 1 : 2 : 4 : 8, ascribing the results to endomitosis or endoamitosis of Heidenhain.

Jacobj's hypothesis of rhythmic nuclear growth is subjected to criticism by Wermel and Ignatieva (1932), who apply statistical methods and conclude that in the multipeaked curves one peak is usually very high and that the cause of the character of these asymmetrical curves is undetermined. In continuation of earlier work by Clara on the effect of poisons on nuclear size in rabbits, they find (1933) that trypan blue and novarsanol cause enlargement of the cells by 30 to 50 per cent or more in frogs and rats, e.g., in liver and kidney. There is said to be a marked increment of chromatin in the nuclei and an increase in the number and size of the nucleoli. None of this work is cytologically critical in showing whether (normally or as a toxic effect) the increase in nuclear volume arises from polyploidy or polyteny, or neither. Biesele, Poyner and Painter (1942) throw light on this relation, which is at least partly due to polyteny (see Chap. XXVI).

Beams and King (1942) show that when two-thirds of the liver is removed from white rats the remaining cells divide rapidly by mitosis. The frequent binucleate cells they find arise from failure of cell division following mitosis. When such binucleate cells undergo a further mitosis two 2 *n* or one 4 *n* nucleus may be produced. Cells were found which were believed to be 16-ploid. This appears to explain the increase in size, at least of liver nuclei, on a polyploid basis, but the long progression of sizes found in different organs requires further elucidation. Undoubtedly polyploidy and polyteny (as in the salivary glands of Diptera) are more important in animal ontogeny than has hitherto been recognized.

Groat (1933) and others find that in leukemia the dividing leucocytes show approximately the haploid number of chromosomes. He studied over 200 mitoses from 12 different cases and found the chromosome number to be usually 24. But in view of the well-known clumping of pairs in human chromosomes, the haploid condition of these leukemic cells can hardly be regarded as proved.

Biesele (1944), in a recent study of nuclear size relations in rat tissues, fails to confirm Jacobj's theory of rhythmic doubling in volume. He finds that in normal tissues the number of plasmosomes remains at six and that the larger chromosomes are not polytenic. It is doubtful. however, whether an increase in the number of nucleoli should be expected in polytene chromosomes. Biesele concludes that the difference in chromosome size from one cell type to another depends on the development of the euchromatin. Organs with larger nuclei, having more euchromatin, also synthesize more enzymes. The increase in mean chromosome volume is also closely paralleled by the total concentration of B vitamins (except inositol) in the cells.

Brummelkamp (1939) finds that the nuclear volume of the neurons in the cerebral cortex varies from species to species of mammals by multiples of $\sqrt{2}$. He also finds that in liver cells, testis interstitial cells and carcinoma cells the nuclear volumes vary in multiples of $\sqrt{2}$. The significance of these relations is obscure. Biesele, Poyner and Painter (1942) throw light on this relation (see Chap. XXVI), which appears to be partly due to polyteny.

LITERATURE

Agar, W. E. 1923. The male meiotic phase in two genera of Marsupials (Macropus and Petauroides). *Quart. J. Micr. Sci.* 67:183–200. Pls. 3.

Ahmed, I. A. 1940. The structure and behaviour of the chromosomes of the sheep during mitosis and meiosis. *Proc. Roy. Soc. Edinb.* 60:260–270. Figs. 12.

———. 1941. Cytological analysis of chromosome behaviour in three breeds of dogs. *Proc. Roy. Soc. Edinb.* 61:107–118. Figs. 19.

Allen, E., Pratt, J. P., Newell, Q. U. & Bland, L. J. 1930. Human tubal ova. *Carneg. Inst. Contrib. to Embryol.* 22:47–75. Pls. 8.

Altmann, S. C. A. & Ellery, M. E. W. 1925. The chromosomes of four species of Marsupials. *Quart. J. Micr. Sci.* 69:463–469. Pls. 2.

Andres, A. H. 1933. Die Riesenzellen in der Spermatogenese des Menschen. *Zeits. f. Zellforsch.* 18:411–434. Figs. 39.

———. 1938. On the chromosome complex in several Canidae. *Cytologia* 9:35–37. Figs. 5.

Andres, A. H. & Jiv, B. V. 1936. Somatic chromosome complex of the human embryo. *Cytologia* 7:371–388. Pl. 1, figs. 22.

Andres, A. H. & Navashin, M. 1935. A morphological analysis of chromosomes in man. *Doklady Acad. Sci. U.S.S.R.* 3:309–312. Fig. 1.

Andres, A. H. & Vögel, J. 1935. Karyological investigation of the embryonal oögenesis in man. *Doklady Acad. Sci. U.S.S.R.* 4:353–354.

———. 1936. Karyologische Studien der Menschenovogenese. I. Embryonale Ovogenese. *Zeits. f. Zellforsch.* 24:552–568. Figs. 16.

Arnold, L. 1912. Adult human ovaries with follicles containing several oöcytes. *Anat. Record* 6:413–422. Figs. 4.

Aykroyd, O. E. 1938. The cytoplasmic inclusions in the oögenesis of man. *Zeits. f. Zellforsch.* 27:691–710.

Beams, H. W. & King, R. L. 1942. The origin of binucleate and large mononucleate cells in the liver of the rat. *Anat. Record* 83:281–296. Pls. 2.

Berger, C. A. 1938. Multiplication and reduction of somatic chromosome groups as a regular developmental process in the mosquito, *Culex pipiens*. *Carneg. Inst. Contrib. to Embryology* 27:209–232. Pl. 1, figs. 10.

———. 1941. Multiple chromosome complexes in animals and polysomaty in plants. *Symposia on Quant. Biol.* 9:19–22.

Berry, R. O. 1941. The chromosome complex of domestic sheep. *J. Hered.* 32:261–267. Figs. 5.

Biesele, J. J. 1944. Chromosome size in normal rat organs, etc. *Cancer Res.* 4:529–539. Figs. 24.

Binder, S. 1927. Spermatogenese von *Macropus giganteus* mit Berücksichtigung einiger allgemeiner Fragen der Säugespermatogenese. *Zeits. f. Zellforsch.* 5:293–346. Figs. 60.

Bishop, D. W. 1942. Germ cell studies in the male fox (*Vulpes fulva*). *Am. J. Anat.* 84:99–114. Pls. 4.

*Bruce, H. A. 1935. The spermatogenetic history in the sheep. *Univ. Pittsburgh Bull.* 32:37–43.

Brummelkamp, R. 1939. Das sprungweise Wachstum der Kernmasse. *Acta Neerl. Morph.* 2:177–187.

Bryden, W. 1932. Cytogenetic studies on the rat. *J. Genet.* 26:395–415. Figs. 17.

———. 1933. The chromosomes of the pig. *Cytologia* 5:149–153. Figs. 10.

Caffier, P. 1931. Das Mesenchymgewebe der menschlichen embryonalen Lunge, besonders auf Wuchsform und Chromosomenbestand hin untersucht. *Arch. f. Exp. Zellforsch.* 11:219–223.

Chruščov, G. 1934. The cultures of blood leucocytes as a method of investigating the somatic karyotype. *Doklady Acad. Sci. U.S.S.R.* 2:498–500.

Chruščov, G. & Berlin, E. A. 1935. Cytological investigations on cultures of normal human blood. *J. Genet.* 31:243–261. Figs. 3, pls. 2.

Chrustschoff, G. K. 1934. Cytological studies of leukocyte cultures in man. *Trudy Medicogenet. Inst. Gorky* 3:213–234 (Russian with English summary.)

Collin, R. & Florentin, P. 1930. Croissance des noyaux en progression géométrique dans la gland de Loewenthal. *Compt. Rend. Acad. Sci. Paris* 191:444–446.

Cox, E. K. 1926. The chromosomes of the house mouse. *J. Morph.* 43:45–53. Pls. 2.

Cross, J. C. 1931. A comparative study of the chromosomes of rodents. *J. Morph.* 52:373–401. Pls. 3.

Cutright, P. R. 1931. Mammalian chromosomes. *Proc. W. Virginia Acad. Sci.* 5:49–51.

———. 1932. The spermatogenesis of the mouse (*Mus musculus* var. *albula*). *J. Morph.* 54:197–220. Pls. 4.

Dreyfus, A. & Campos, J. E. de S. 1939. Os cromosomas na espermatogenese de *Didelphys aurita* (Wied). *Univ. São Paulo Bol. Fac. Filos. Cien. e Letras, Biol. Geral* 17:3–19. Pls. 4.

Drummond, F. H. 1933. The male meiotic phase in five species of marsupials. *Quart. J. Micr. Sci.* 76:1–11. Pls. 2.

Evans, H. M. & Swezy, O. 1929. The chromosomes in man; sex and somatic. *Mem. Univ. Calif.* 9: No. 1. Pp. 64, pls. 11.

Fankhauser, G. 1940. A pentaploid larva of the newt. *Proc. Nat. Acad. Sci.* 26:526–532. Figs. 9.

———. 1941. Polyploidy in salamanders. *Proc. Edinb. Genet. Congr.* P. 118.

———. 1945. The effects of changes in chromosome number on Amphibian development. *Quart. Rev. Biol.* 20:20–78. Figs. 7.

Freerksen, E. 1933. Ein neuer Beweis für das rhythmische Wachstum der Kerne durch vergleichende volumetrische Untersuchungen an den Zellkernen von Meereschweinchen und Kaninchen. *Zeits. f. Zellforsch.* 18:362–399.

Frolova, S. 1929. Die Polyploidie einiger Gewebe bei Dipteren. *Zeits. f. Zellforsch.* 8:542–565. Pl. 1, figs. 18.

Gates, R. R. 1939. Nucleoli, satellites and sex chromosomes. *Nature* 144:794.

Gates, R. R. 1942a. Nucleoli and related nuclear structures. *Bot. Review* 8:337–409.

———. 1942b. Chromosome numbers in Mammals and Man. *Science* 96:336–337.

Generales, K. D. J. 1937. Mikropathologie der Spermatozoen bei Erbkranken. *Zeits. Abst. u. Vererb.* 73:483–488.

Greenwood, A. W. 1923. Marsupial spermatogenesis. *Quart. J. Micr. Sci.* 67:203–216. Pls. 2.

Groat, W. A. 1933. Leukemias showing haploid leukoblasts undergoing mitotic division in circulating blood. *Am. J. Med. Sci.* 185:624–629. Pls. 2.

Haase-Bessell, G. 1936. Kernsymbiose-Polyploidie in Beziehung auf menschliche Verhältnisse. *Zeits. f. Mensch. Vererb. u. Konst.* 20:78–89.

Hamilton, W. J. 1944. Phases of maturation and fertilization in human ova. *J. Anat.* 78:1–4. Pls. 2.

Hance, R. T. 1917. The diploid chromosome complexes of the pig (*Sus scrofa*) and their variations. *J. Morph.* 30:155–222. Pls. 10, figs. 5.

Hertwig, G. 1935. Die Vielwertigkeit der Speicheldrüsenkerne und -chromosomen bei *Drosophila melanogaster*. *Zeits. f. Abst. u. Vererb.* 70:496–501. Figs. 5.

Husted, L., Hopkins, J. T. Jr., & Moore, M. B. Jr. 1945. The X-bivalent of the golden hamster. *J. Hered.* 36:93–96. Figs. 3.

Jacobj, W. 1935. Die Zellkerngrösse beim Menschen. *Zeits. f. mikr.-anat. Forsch.* 38:161–240.

Kemp, Tage. 1929. Über das Verhalten der Chromosomen in den somatischen Zellen des Menschen. *Zeits. mikr.-anat. Forsch.* 16:1–20. Figs. 22.

———. 1930. Über die somatischen Mitosen bei Menschen und warmblutigen Tieren unter normalen und pathologischen Verhältnissen. *Zeits. f. Zellforsch.* 11:429–444. Figs. 27.

Kennedy, W. P. 1924. The occurrence of polyovular Graafian follicles. *J. of Anat.* 58:328–334. Figs. 8.

King, R. L. & Beams, H. W. 1936. The sex chromosomes in man, with special reference to the first spermatocyte. *Anat. Record* 65:165–174. Pl. 1, fig. 1.

Koller, P. C. 1936. Chromosome behaviour in the male grey squirrel (*Sciurus carolinensis leucotus*). *Proc. Roy. Soc. Edinb.* 56:196–209. Figs. 12.

———. 1937. The genetical and mechanical properties of sex chromosomes. III. Man. *Proc. Roy. Soc. Edinb.* 57:194–214. Figs. 12, pls. 2.

———. 1938. IV. The golden hamster. *J. Genet.* 36:177–195. Figs. 12, pl. 1.

———. 1941. The genetical and mechanical properties of the sex chromosomes. VIII. The cat (*Felis domestica*). *Proc. Roy. Soc. Edinb.* 61:78–94. Figs. 27.

Koller, P. C. & Darlington, C. D. 1934. The genetical and mechanical properties of the sex-chromosomes. *J. Genet.* 29:159–173. Figs. 17, pl. 1.

Krallinger, H. F. 1927. Die Chromosomen der Haustiere. *Züchtungskunde* 2:441–466.

*———. 1931. Cytologische Studien an einigen Haussäugetieren. *Wiss. Arch. Landwirts. Abt. B.* 5:127–187. Figs. 18.

———. 1936. Die Chromosomen des Halsbandpekaris (*Pecari tajacu*). *Zeits. f. Zellforsch.* 24:1–10. Figs. 8.

League, B. B. 1928. The chromosomes of the guinea-pig. *J. Morph.* 46:131–138. Pls. 2.

*Levit, S. G. 1934. On cytological abnormalities in man. *Proc. Med.-Biol. Inst. Moscow* 3:235–238. Figs. 2.

McClung, C. E. 1939. Chromosome numbers in animals. *Tab. Biol.* 18:1–60.

Matthey, R. 1938. Contribution nouvelle à l'étude des hétérochromosomes chez les mammifères, et singulièrement chez les rongeurs. *J. Genet.* 36:73–102. Pls. 5, figs. 6.

Minouchi, O. 1928a. Spermatogenesis of the albino rat (*Mus norvegicus albus*). *Jap. J. Zool.* 1:235–254. Pls. 2.

———. 1928b. The spermatogenesis of the dog, with special reference to meiosis. *Jap. J. Zool.* 1:255–268. Pl. 1.

———. 1928c. On the chromosomes of the domestic mouse (*Mus wagneri* var. *albula*). *Jap. J. Zool.* 1:269–273. Pl. 1.

———. 1929. On the spermatogenesis of the raccoon dog (*Nyctereutes viverrinus*), with special reference to the sex-chromosomes. *Cytologia* 1:88–108. Pls. 2.

Minouchi, O. & Ohta, T. 1934. On the number of chromosomes and the type of sex-chromosomes in man. *Cytologia* 5:472–490. Figs. 26.

Nicholas, J. S. & Hall, B. V. 1942. The development of isolated blastomeres and fused eggs. *J. Exp. Zool.* 90:441–459. Pl. 1.

Oguma, K. 1930. A further study of the human chromosomes. *Arch. de Biol.* 40:205–226. Figs. 5.

———. 1934. A new type of the mammalian sex-chromosomes, found in a field mouse, *Apodemus speciosus*. *Cytologia* 5:460–471. Figs. 14.

———. 1937. The segmentary structure of the human X-chromosome compared with that of rodents. *J. Morph.* 61:59–93. Pls. 3, figs. 6.

Oguma, K. & Kakino, S. 1932. A revised check-list of the chromosome number in Vertebrata. *J. Genetics* 26:239–254.

Oguma, K. & Kihara, H. 1923. Étude des chromosomes chez l'homme. *Arch. de Biol.* 33:493–514. Pls. 3.

Painter, T. S. 1922. Spermatogenesis of the opossum (*Didelphis virginiana*). *J. Exp. Zool.* 35:13–45. Pls. 3, figs. 8.

———. 1923. The spermatogenesis of man. *J. Exp. Zool.* 37:291–334. Pls. 6. figs. 4.

———. 1924. The chromosomes of the horse. *J. Exp. Zool.* 39:229–247. Pls. 2.

———. 1924. The sex chromosomes of man. *Amer. Nat.* 58:506–524. Figs. 22.

———. 1924. The sex chromosomes of monkeys. *J. Exp. Zool.* 39:433–460. Pls. 5, fig. 1.

Painter, T. S. 1925. A comparative study of the chromosomes of mammals. *Amer. Nat.* 59:385–409. Pl. 1, figs. 8.

———. 1926. The chromosomes of the rabbit. *J. Morph.* 43:1–22. Pls. 8, fig. 1.

———. 1940. A review of some recent studies of animal chromosomes. *J. Roy. Micr. Soc.* 60:161–176. Figs. 4.

Saez, F. A. 1931. The chromosomes of the South American opossum, *Didelphis paraguayensis*. *Amer. Nat.* 65:287–288. Figs. 2.

———. 1938. Investigaciones citólogicas sobre los marsupiales sudamericanos. *Rev. Soc. Argentina Biol.* 14:156–161. Figs. 2.

Sanderson, Ann. 1933. The cytology of parthenogenesis in Tenthredinidae. *Genetica* 14:321–455. Pls. 19.

Schachow, S. D. 1926. Über die Chromosomenzahl in den somatischen Zellen des Menschen. *Anat. Anz.* 62:122–127. Figs. 4.

Shiwago, P. I. & Andres, A. H. 1932. Die Geschlechtschromosomen in der Spermatogenese des Menschen. *Zeits. f. Zellforsch.* 16:413–431. Figs. 17.

Smith, E. C. 1940. Sex expression in willows. *Bot. Gazette* 101:851–861. Figs. 4.

Srinath, K. V. 1939. Morphological and cytological studies in the genus *Calceolaria*. *Zeits. f. Abst. u. Vererb.* 77:104–134. Figs. 108.

Swezy, O. 1927. The chromosomes of the rat. *Science* 66:601–602. Figs. 3.

Swezy, O. & Evans, H. M. 1930. The human ovarian germ cells. *J. Morph.* 49:543–577. Pls. 5.

Tateishi, S. 1937. On the chromosomes of two species of Insectivora. *Jap. J. Genet.* 13:211.

Varela, M. E. & Saez, F. A. 1934. Un nuevo método para el estudio de los cromosomas somáticos del hombre. *Rev. Soc. Argentina Biol.* 10:421–422.

Wermel, E. M. & Ignatieva, Z. P. 1932. Über die Grössenvariabilität der Zellkerne verschiedener Gewebearten. *Zeits. f. Zellforsch.* 16:674–688.

——— & ———. 1933. Über die Veränderungen der Kerngrösse bei Vergiftungen. *Zeits. f. Zellforsch.* 17:476–504. Figs. 19.

Wieman, H. L. & Weichert, C. K. 1936. An unusual double human pregnancy with a single corpus luteum. *Anat. Record* 65:201–206. Pls. 2, figs. 2.

Wilkinson, J. 1941. The cytology of the cricket bat willow (*Salix alba* var. *caerulea*). *Ann. of Bot.* N.S. 5:149–165. Figs. 20.

Winiwarter, H. de. 1912. Études sur la spermatogenèse humaine. *Arch. de Biol.* 27:91–189. Pls. 2.

———. 1934. La formule chromosomiale chez diverses races de chats (*Felis domest.*). *Acad. Roy. Belg. Bull. Cl. Sci.* 20:512–518. Pl. 1.

Winiwarter, H. de & Oguma, K. 1926. Nouvelles recherches sur la spermatogenèse humaine. *Arch. de Biol.* 36:99–166. Pls. 2.

Wipf, L. & Shackelford, R. M. 1942. Chromosomes of the red fox. *Proc. Nat. Acad. Sci.* 28:265–268.

Wodsedalek, J. E. 1931. Spermatogenesis of the red fox, *Vulpes fulvus* (Abstr.). *Anat. Rec.* 51:70.

Yeager, C. H., Painter, T. S. & Yerkes, R. M. 1940. The chromosomes of the chimpanzee. *Science* 91:74–75. Fig. 1.

Zuitin, A. I. 1935. On the chromosomes of the yak. *Doklady Acad. Sci. U.S.S.R.* 4:81–83.

———. 1938. New data on the chromosome number in yak (*Poephagus grunniens* L.). *Doklady Acad. Sci. U.S.S.R.* 19:201–202. Figs. 3.

Chapter IV

LINKAGE

THE first case of genetic linkage was discovered in the sweet pea by Bateson and Punnett in 1906. As a result of the work of Morgan and his school with *Drosophila melanogaster* it was clear by about 1910–1915 that the number of linkage groups corresponds with the number (4) of chromosome pairs. Punnett (1923) found in the sweet pea, with $n = 7$ chromosome pairs, that there were 7 (or 8) linkage groups. In maize, with $n = 10$, 10 linkage groups are well known. Schick (1934) showed that in the snapdragon with $n = 8$, the 68 tested genes fall into 8 linkage groups, while MacArthur (1934) found that in the tomato ($n = 12$) 20 genes were located on 10 different chromosomes. In several other species of Drosophila (*D. Willistoni* $n = 3$, *D. pseudoöbscura* $n = 5$, *D. virilis* $n = 6$) the number of linkage groups is known to correspond with the chromosome number. This correspondence was one of the final proofs of the chromosome theory. Clark (1935) found a genetic marker for a fourteenth chromosome in the mouse, in which 16 characters had been tested and $n = 20$, but Grüneberg (1943) recognizes only 8 linkage groups. Castle (1940) lists 19 loci in 4 different chromosomes (linkage groups) of the rabbit ($n = 22$), one locus having as many as 6 multiple alleles. Once marker genes are known for many different chromosomes it becomes relatively easier to fill in the map by tests of further genes. In the fowl, Hutt and Lamoreux (1940) show that 23 gene mutations belong in 6 linkage groups, 8 of these genes being in the X-chromosome, which has been identified by its small V-shape. Mather (1938) has given an account of the general principles of linkage measurement.

Extensive chromosome maps of these and other organisms are now in existence and still growing, the relative positions of the genes in a chromosome being determined by the frequency of crossing-over between them, whereas genes in different chromosome pairs show free assortment, with ordinary Mendelian ratios of the pairs of characters involved. In man there should ultimately be 24 linkage groups, but it will probably be a long time before marker genes are known for all 24 pairs of chromosomes. Many more or less certain cases of linkage are referred to in later chapters. A list is given at the end of this chapter, and a number of other possible cases require further testing. Before any character can be accepted as marking a new linkage group, it must be tested with at least one member of every linkage group already known, so a chromosome map can be built up only very gradually. It is of course an advantage that the genes used as markers in man should be common ones, and so in recent years efforts have been made to determine whether there was linkage between various genes of widespread or universal occurrence. In small human families the coupling and repulsion phases are not readily distinguished. Coupling of course occurs when both the genes being tested are in the same chromosome, and repulsion when one is in each member of a pair.

As with animals, the first cases of linkage in man were between sex-linked characters. Such characters, being linked with sex (i.e., in the X-chromosome), are naturally also linked with each other. Madlener (1928) discovered a family in which hemophilia and color-blindness were both present in three males (see Fig. 217, p. 594). Bell and Haldane (1937) give further information about this family. Before considering the more intricate problems connected with sex-linkage, we may take up the present evidence regarding non-sex-linked or autosomal characters in man. With a view to constructing chromosome maps, it is almost equally important to show that any two factors are linked or that they are definitely not linked. Snyder (1926) showed that various claims of linkage between particular diseases and the blood groups were not on a sound statistical basis. At the same time he determined the probable independence of eye color, the blood groups and recessive polydactyly; also of telangiectasis and the blood groups. Attempts have been made to show linkage even between the blood groups and hemophilia, although the former are autosomal and the latter in the X-chromosome!

There has been continual advance in methods of detecting linkage. Bernstein (1931), using the blood groups, first pointed out that linkage could be detected and estimated from data of parents and children only, thus making possible the construction of human chromosome maps. Employing statistical methods, he confirmed the opinion of Landsteiner and Levine that the AB blood groups are independent of the MN blood types (see Chap. XVI). Wiener (1932) pointed out that in such families the offspring can be divided into three classes: linked, cross-overs, and indeterminates, the last being discarded in the analysis. The frequencies of the other two classes can then be compared with the expectation for various assumed linkage intensities, and the linkage determined in this way. Hogben (1934) introduced refinements into these methods. When dominance is complete, the following three classes of matings give the proportions of phenotypes which depend on crossing-over values:

1. **AaBb** × **aabb**
2. **AaBb** × **Aabb** (or **AaBb** × **aaBb**)
3. **AaBb** × **AaBb**

Bernstein showed from (1) and (2) how to determine linkage when **Aa** is distinguishable from **AA,** and **Bb** from **BB,** but in man they are generally indistinguishable or the character of the homozygote is unknown. Hogben derived a more general expression and drew up tables for testing the gene linkage. He points out that since rare dominant genes can be assumed to be all heterozygous without serious error, Bernstein's product method can be used to assign a cross-over value regardless of either inbreeding or homogamy (mate selection). This is not true of rare recessives, in which the method will detect linkage but not cross-over values.

Haldane (1934) extended these methods for detecting autosomal linkage, including the case of three allelomorphs, and developed a number of new formulae for linkage of various types of autosomal genes. Two of these apply to the linkage relations of a rare dominant. His paper applies the principles of statistical estimation comprehensively to the problems of linkage in man. Fisher (1934a) compares the proband method with the sib method of collecting family data for statistical purposes. The proband method is valid only for data in which ascertainment is complete within definite limits of space and time, i.e., where the condition of all the members in a pedigree is ascertained. The sib method is of wider application where ascertainment is imperfect, provided that frequencies are based on the number of individuals rather than the number of families. Formulae are given for use with both methods. Fisher (1934b) shows how the limitations of Haldane's methods can be determined, and that the amount of information regarding linkage derived from family records can be calculated from the theoretical frequencies of different kinds of families or paternal gene combinations, expressed in terms of the linkage value to be estimated. In another paper (1934c) he shows how the process of simultaneous estimation is a still better method when the two types of double heterozygotes are for any reason unequal or uncertain, or when information is available regarding the grandparents. In another note, Fisher (1939) discusses methods of estimating linkage between autosomal genes and the effects of differential viability, developing expressions for close or loose linkage in the coupling or repulsion phases.

In a further paper, Fisher (1935a) points out that for dominant genes all types of family but one are adequately treated by Haldane's method, using Bernstein's method of scoring families. He gives an alternative *u* statistic for scoring back-cross families, which is applicable to all cases and enables families of different size to be combined. For the detection of linkage of recessive genes (Fisher 1935b) allowance has to be made for the selection of families having one or more affected children, because in small families two normal parents may both be heterozygous and yet have no affected children. Families can be used in which one or both parents are unknown, with relatively little loss. Mather and Philip (1940) used linkage with marker genes to determine whether harelip and cleft palate — a condition with incomplete penetrance — is represented by different complementary or analogous genes, in different pedigrees (see p. 822), i.e., whether all forms of harelip are determined by the same gene.

Snyder, Burks and Penrose independently realized that data for linkage could be derived from one generation only. Penrose (1935) showed that it was possible to determine autosomal linkage from sibs alone, without any knowledge of the parents. Children can thus be examined in schools and other institutions. His paired sib method is based on the principle that, when pairs of sibs are taken at random from a series of families, certain types of sib pairs will be more frequent if there is linkage than if there is free assortment of the characters studied. He applied this simple and effective method to sixty sibling pairs on which records were made of (1) the ABO blood groups, (2) blue eyes, (3) bright red hair (regarded as a simple recessive, with reddish hair and freckles as the heterozygote). The blood groups were independent of eye color, and red hair was independent of blue eyes; but a random distribution of red hair and blood group A would only give the results obtained once in thirty times, so there is a possibility of linkage of these two genes.

Fisher (1935b) pointed out that the value of the data from large families would be much enhanced by scoring the families individually instead of classifying all the sib pairs in a fourfold table. Finney (1941a, b), using Boyd's (1941) blood group and taste data, shows how partial information regarding a character in parents can be utilized in addition to that from sibs, in determining linkage. The efficient score is the sum of the scores for every possible mating which could show crossing-over in the offspring, each multiplied by the probability that these matings were the true ones. He gives expressions also for families in which parental testing is incomplete for one gene only. In this way a fivefold increase in precision may be obtained; but there is still no indication of linkage between the genes for (1) **ABO,** (2) **MN** and (3) taste-blindness (**Tt**) or between any of these and sex. Snyder, Baxter and Knisely (1941), using the method of sib pairs on 64 sibships, confirmed the independent inheritance of the blood groups, the blood types and taste reaction to PTC. Finney (1942) extends this principle of efficient scoring systems to the determination of linkage from sibships only. The new technique involves considerably more labor in computation than the simple method of paired sibs, but the latter yields only 20 to 70 per cent of the information regarding linkage which can be derived from the new method. There is a marked advantage in including the parents whenever possible. Wiener (1943, p. 375) points out that the paired sib method necessarily includes many sibships which can yield no information regarding linkage.

In human families generally only two generations are available for examination and it is usually impossible to state whether two genes for which a parent is heterozygous are in coupling or repulsion (i.e., whether they are both in the same chromosome or one in each member of a pair). Hence the children cannot be classified as cross-overs or non-cross-overs. To overcome this difficulty, Finney (1943) combines the evidence from different families, assuming that coupling and repulsion are equally frequent and applying the principles of efficient scoring to the problem.

Hogben and Pollack (1935) tested the ABO blood groups and. the ability to taste phenylthiocarbamide (**Tt**) in sibs and parents of fraternities containing individuals having (*a*) Friedreich's ataxia and (*b*) brachydactyly. In Drinkwater's brachydactyl families the number of brachydactyls had increased from 49 to 63. While the numbers tested were not large enough to give a definite result, no evidence was found of linkage between Friedreich's ataxia and taste-blindness or blood groups, nor of linkage between brachydactyly and these two conditions. Probably the blood-group locus, that for taste-blindness and for Friedreich's ataxia, are all in different chromosomes. There is still the possibility that brachydactyly and Friedreich's ataxia might be linked. Fisher (1936a), in a criticism of Hogben and Pollack's paper, shows that while the numbers tested were not large enough to show linkage if it existed, yet by testing for homogeneity of data, one family, unlike the other eleven, has a constitution strongly favoring linkage of Friedreich's ataxia with the blood groups.

By applying the χ^2 test to randomly collected sibships tested for taste reaction to PTC, Cotterman (1937b) shows that the character is behaving as a unit. This test can be applied to the data where there is any doubt about the genic nature of the character studied.

Various instances of presumed autosomal linkage, such as that between eye color and hair color, are known. Beadle (1926) observed in a family that those with certain missing teeth were mostly dark haired (see p. 358). He suggested 10 per cent of crossing-over in the male. Tomesku's pedigree (Fig. 145, p. 412) shows linkage between clinodactyly and brunet complexion. Burks (1937), following this clue, found that in various other families congenital absence of certain teeth is linked with hair color, the estimated rate of crossing-over being 13 to 15.5 per cent. She also found evidence in families of linkage between myopia and eye color. In a further account (Burks, 1938) the recombination ratio was found to be about 0.10. In a fuller study (Burks, 1941) of fifteen families from data in the Eugenics Record Office and fourteen other families obtained through clinics and visited in the field, the latter were X-rayed to determine the congenital absence of teeth, and only children over fifteen years old were included. Contrary to dental opinion, congenital missing third molars (wisdom teeth) are attributed to the same factor which determines missing incisors and premolars. The deficiencies are irregularly distributed in the jaw, like the missing bristles in Drosophila in the presence of the genes dichaete, hairless, scute and echinus. Probably in some pedigrees missing third molars is the simplex (heterozygous) condition and missing anterior teeth the duplex condition. The relation of peg or rice teeth to missing teeth was not clear. Undersized lateral incisors appeared to be linked to hair color, but it was not determined whether this condition is another gene allelic to deficient anterior teeth or a simplex expression of the same gene. Using the method of like and unlike sib pairs, and applying the χ^2 test to fourfold tables of sib concordance and discordance in tooth deficiency and hair color, Burks found a recombination ratio of 0.10 for the E.R.O. material and 0.025 for the field data. Possibly this difference may be connected with differences in ascertainment.

Nielson (1940), in a note, cites a family in Utah in which three out of sixteen children in a sibship have albinism combined with certain ocular defects not associated with albinos. Finney (1941c) found that twenty-six out of sixty-six families from the data of Zieve, Wiener and Fries could be used as evidence of linkage between the ABO blood groups and allergy, with a recombination value of 22.8 per cent.[1] Munro, Penrose and Taylor (1941) analyzed twenty-five sibships by the sib-pair method and found some evidence of linkage between ABO and phenylketonuria. Race, Taylor and Vaughan (1941) tested patients with acholuric jaundice for possible linkage with ABO, MN, AB in the saliva (secretor factor), taste for PTC, iris color, attached or free ear lobes and hair color. If this battery of tests can be carried out on sufficient numbers, they should give further valuable evidence regarding the linkage of some common genes.

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[1] Bernstein et al. (1943) find this claim of linkage unjustified. They also find that the MN blood types are probably independent of allergy.

Penrose (1938) has developed a method for detecting linkage between graded or quantitative characters. From recorded data on the grades of two characters in pairs of sibs, the degree of linkage can be determined. He shows that the estimation of linkage in characters without dominance in a random population is independent of gene frequency. These methods can also be adapted for the study of dominant or recessive characters.

We may now pass to the consideration of *sex-linkage.* Davenport (1930) cited fourteen sex-linked genes in the X-chromosome and looked for cases of linkage between them. He collected a number of families with hemophilia, in one of which (the Gross family) color-blindness was also present, but no individual had both. In this family, in four generations there were 8 cases of color-blindness (7 ♂ 1 ♀) and 4 of hemophilia. One woman had two sons with hemophilia and two color-blind sons as well as three normal daughters. It would be supposed that one of her X-chromosomes carried **h** (hemophilia) and one **c** (color-blindness). But her father was normal and all her ancestors and relatives were free from hemophilia. Hence probably the **h** gene arose as a mutation in one of her father's germ cells, although the possibility is not excluded that she was a mosaic resulting from somatic mutation in her ovarian tissue. Bell and Haldane (1937) calculate the probability of a mutation in this case as *ca.* 0.00025 or 4000 : 1. Levit (1936) found about eleven genes located in the X-chromosome.

Characters will be completely sex-linked only when they remain always in the X- or the Y-chromosome. In previous chapters we have seen from the cytological evidence that the X and Y have (1) certain homologous portions between which crossing-over can take place, (2) certain non-homologous portions, and (3) a large portion of the X has no homologue in the shorter Y. It is clear that the sex-determining part of the X must be that part in which there is normally no crossing-over, but it is possible that some human intersexes may arise through occasional crossing-over in this region. Crossing-over between the sex chromosomes is already well known in three genera of cyprinodont fishes (Aida, 1930; Winge, 1923), in which the X and Y are not visibly differentiated from the autosomes. Morgan (1926) suggested that in Lebistes the X consists of an autosomal part in which crossing-over takes place and a sex-determining part in which crossing-over is excluded. Winge (1934) has shown that each of the autosomes contains factors making for masculinity or femininity. By selected crossings it was thus possible to accumulate them and obtain males that were XX instead of XY, as well as XY females and YY males. The allelic series of eighteen male-sex-linked genes for color patterns were found to be constantly located at one end of the Y, in the same locus as the very strong male sex factor of the Y. Winge's view is that this male gene at the same time produces one of the series of color patterns. In that case it would be pleiotropic in its effect; but it is possible that the color gene locus is so close to the male gene that crossing-over rarely or never occurs between them. In fact it is difficult to believe that two such different effects as sex and a specific color pattern can be produced by the same gene. In any case it is clear that the XY mechanism in fishes is less stabilized than in mammals, although intersexes seldom occur.

Crossing-over between the X and Y, although rare in Drosophila, has been observed by Philip (1935) in *D. melanogaster*. Both double crossing-over and inverted crossing-over were found, the frequency being only 1 in 3000. The locus for bobbed bristles, which crossed over, was found to be near the end of the region common to X and Y, probably at the distal end. Bobbed is thus partially sex-linked.

In an important paper on *incomplete sex-linkage* in man, Haldane (1936) developed statistical methods for detecting such partial linkage and obtained more or less definite evidence that the following six conditions were in this category: xeroderma pigmentosum (recessive), achromatopsia (total color-blindness, recessive), retinitis pigmentosa (the recessive form not associated with deafness and not completely sex-linked), retinitis pigmentosa (dominant form, in some pedigrees), Oguchi's disease (recessive), epidermolysis bullosa dystrophica (recessive form). These conditions are all discussed in later chapters. The two forms of retinitis pigmentosa may be alleles, but there is no certainty about this. It will be seen that five of these conditions are recessive, one dominant. Also four of them pertain to the eye, two to the skin; all are ectodermal, but this may be only chance.

If a gene **A** is located in the part of the X which is homologous with the Y, then a heterozygous female will be of the constitution **AX** · **aX** and any crossing-over which may occur between her X-chromosomes will not show in her offspring. A heterozygous male will be of the constitution **aX** · **AY** if he inherited **A** from his father, and **AX** · **aY** if he got the **A** from his mother. With a limited amount of crossing-over, **A** will thus be transmitted by the male preferentially to those of his children who are of the same sex as the parent from whom he derived it. If a male is **aX** · **AY,** most of his sons will receive the **A** gene, if **AX** · **aY,** most of his daughters will receive it. Phenotypically of course the two genotypes **aX** · **AY** and **AX** · **aY** are indistinguishable.

On the basis of the cytological results, especially of Koller (1937), and the genetical results of Haldane, we have sketched in Fig. 23 a tentative map of the X- and Y-chromosomes, showing the relative positions of satellites and centromeres and roughly the relative lengths. The X is about three times the length of the Y, about two-thirds of it is non-pairing, and the centromere is so placed that the shorter arm (inner segment) is one-fifth to one-third that of the longer arm (outer segment). The occurrence of chiasmata in both arms indicates that the length of the pairing (homologous) segment is over fifty cross-over units. Hence genes located at the ends of this segment should show very little sex-linkage. Haldane drew up a tentative map of the human X-chromosome (see Fig. 23), based on cross-over values, but as these are still subject to considerable uncertainty, the order of some of these genes may be changed, and some may even be found not to cross over.

In a discussion of this work, Fisher (1936b) points out the need for accuracy and completeness in recording the sex and relationship of all persons both affected and normal, in pedigrees, in order to obtain linkage data. He shows how, with three different methods of treatment, using ancillary information or assuming single or complete ascertainment, the "order" of at least four of these genes would be changed. To the map have been added five genes in the non-homologous part of the X. They are Leber's optic atrophy, near the junction of the two parts of the X, hemophilia, deuteranopia and protanopia, myopia.

Recessive spastic paraplegia (Haldane, 1941) has since been added to the list of partially sex-linked genes, but its position in relation to other genes in the X is unknown.

In the case of partially sex-linked recessives it can easily be shown that the 3 : 1 ratio in sibships will be disturbed, and there will be an excess of some classes and a deficiency in others. In other matings, where the gene was received by the father from the other paternal grandparent, the distortions will be in the opposite direction. If, for instance, in the non-cross-overs the daughters are all **a** and the sons half **A,** in the cross-overs the daughters will be half **A** and the sons all **a**.

Burks (1937) criticized Haldane's results with retinitis pigmentosa. To the 89 sibships used by him she added 25 from the Eugenics Record Office and 40 from other sources, making a total of 154. The fuller data and certain corrections lead to the conclusion that dominant retinitis pigmentosa (*q.v.*) shows partial sex-linkage, although Haldane's two-gene hypothesis of one dominant autosomal and one incompletely sex-linked gene requires further test. For recessive retinitis pigmentosa with deafness, Haldane's provisional negative conclusion is corroborated. In some of these families the deafness is partial, in some it is complete and congenital, in some all the cases of retinitis pigmentosa are deaf and none of the unaffected are deaf; in others, deafness or retinitis pigmentosa can occur separately in a pedigree. Hence there may be two independent or linked genes, for retinitis pigmentosa and for deafness. The question of linked genes or variable expressivity arises in acute form in some of the medical syndromes.

In making her calculations, Burks used Fisher's (1936b) device allowing for the method of ascertainment. For recessive retinitis pigmentosa without deafness, which is sex-linked in 15 per cent of pedigrees, the fuller data lead to the conclusion that there is no evidence of partial sex-linkage. Haldane (1941b) has since added three new pedigrees of retinitis pigmentosa, bringing the number of children of affected males up to 314 with 143 cross-overs.

Another probable case of partial sex-linkage was cited by Haldane (1938) in Snell's (1903) pedigree of retinitis pigmentosa (Fig. 76, p. 211). Analysis of this pedigree shows the following types of transmission:

Grandfather	→	father	→	son	6
Grandfather	→	father	→	daughter	2
Grandfather	→	mother	→	son	3
Grandfather	→	mother	→	daughter	2
Grandmother	→	father	→	son	1
Grandmother	→	father	→	daughter	7
Grandmother	→	mother	→	son	2
Grandmother	→	mother	→	daughter	4

Thus the ratio is, grandparent to grandchild of same sex, 20; grandparent to grandchild of different sex, 7, — a ratio which is far from equality. This indicates the usual transmission through the X, but occasional crossing-over between the X and Y in the male, and also no doubt between the two X's in the female, although the latter will not affect the result.

Bell and Haldane (1937) considered the crossing-over relations between color-blindness and hemophilia. The pedigrees used were two new ones and that of Madlener, all of which showed coupling, and those of Birch and of Green (the latter in Davenport, 1930) which showed repulsion, as well as that of Riddell. The form of color-blindness was deuteranopia (green-blindness). The genes for hemophilia and deuteranopia were shown to be closely linked, with a cross-over frequency of *ca.* 5 per cent. Only one actual (not quite certain) case of crossing-over occurred in these pedigrees however. Since these two genes never cross over from the X to the Y, they must be located in the non-homologous part of the X-chromosome. In three of the six pedigrees the hemophilia appears to have originated as a mutation, and there is much other evidence (see Chap. XIV) of the mutational origin of this disease.

Rath (1938) used two large pedigrees of hemophilia to test crossing-over. One was Günder's pedigree with about eight hundred descendants of a single pair in the Saar; the other was the Calmbach pedigree in Wurtemburg. They were investigated for red-green color-blindness. None was found among nearly one hundred members of the Günder family who were tested, but in the Bott-Barth family of Schloessmann it was found in different combinations with hemophilia. A woman, who received the gene for hemophilia from her father, also transmitted color-blindness, which apparently arose as a mutation, since there was no evidence of color-blindness in her ancestry. She had four sons, one showing both conditions, one normal, one with hemophilia only and one with color-blindness only. Whether the color-blindness was in the same X-chromosome as hemophilia or in the other X, crossing-over must therefore have occurred.

Riddell (1937, 1938) found the two conditions present in a family in the west of Scotland. One woman was heterozygous for both, having derived hemophilia from her father and color-blindness from her mother's father. Her two X-chromosomes could be represented $\frac{\mathbf{c}\ +}{+\ \mathbf{h}}$. Her only son has **c** but not **h**, so there was no crossing-over. Her sister was almost certainly $\frac{+\ +}{+\ \mathbf{h}}$, as she had three sons, one of whom was hemophilic while the other two were normal. In an addendum, Haldane concludes from this and previous evidence that the cross-over value is ± 4.5 per cent.

White (1940) finds color-blindness (deuteranopia) associated with a gene for congenital stationary night-blindness with myopia in a pedigree of seven generations and 273 individuals, of whom 183 (87 ♂ 96 ♀) are in the direct line of descent. Thirteen of the females were transmitters, nine more may become so, and twenty male descendants show ocular defects. All were descended from a Mr. Shurly, born 1760–1780. The three sex-linked conditions were all transmitted by one woman (III. 1) in the pedigree, to her male descendants. The night-blindness (which could not be cured by large doses of vitamin A) is either tightly linked to myopia or both conditions are due to one gene. The latter supposition is improbable, as both are inherited singly in other pedigrees. There is a high rate of crossing-over between this locus and that for color-blindness and Haldane calculates the rate of crossing-over at 43.25 ± 4.15 units. Indeed, if both were not sex-linked they might be regarded as in separate chromosomes. These genes are clearly in the non-homologous part of the X, since there is no crossing-over to the Y.

Hogben (1932) has made an interesting analysis of the mathematical correlation between various relatives, such as grandparents, aunt and uncle and cousins, in cases of a sex-linked gene, where the families have been selected because at least one child is affected. Snyder (1934) shows that a random survey of a population containing a recessive sex-linked gene such as color-blindness will yield two separate estimates of frequency, from the proportion of affected males and of affected females. A comparison of these two statistics gives a test of whether the gene is sex-linked. Cotterman (1937a) developed formulae for the detection of sex-linkage in families collected at random.

Finney (1939) used Sir Francis Galton's records of stature in an attempt to determine statistically whether there are any sex-linked factors which influence stature. Large differences were found in parent-child correlations, but the data did not yield any clear evidence that such factors do or do not exist.

Fortuyn (1939) points out that in the case of a gene like color-blindness the number of affected males and of heterozygous females is not necessarily the same, because a color-blind male could receive his defective chromosome from a heterozygous or a homozygous mother, while a heterozygous female could also have it from a color-blind father. If the two male genotypes are represented by X and x, the three female genotypes will then be XX, Xx and xx. In a population without selection, the five types will become stabilized and will show rather simple relations. These should be useful in determining the gene frequency of any sex-linked character in a population. In the absence of fresh mutations, the frequency of color-blindness should remain constant, and Danforth (1924) found no evidence of change in fifty years. If $a = \%$ normal ♀♀ (XX), $b = \%$ heterozygous ♀♀ (Xx) and $c = \%$ normal ♂♂; then $a = \frac{2ac + bc}{200}$, $b = \frac{200a + 100b + 200c - 4ac - 2bc}{200}$, $c = \frac{2a + b}{2}$. It may be deduced that in terms of c (the percentage of normal males) $a = \frac{c^2}{100}$ and $b = 2\left(c - \frac{c^2}{100}\right)$. A table is given, from which the composition of stable populations with various frequencies of normal males can be determined. The percentage of normal and affected males, and of homozygous (normal or affected) females may vary between 0 and 100, but in a stable population the heterozygous females will never exceed 50 per cent. It is often supposed that in a freely breeding population linked genes can be recognized by the usual association of the corresponding characters. This is not so, however, but (except in the case of complete linkage) linked genes tend to become independently distributed in the population.

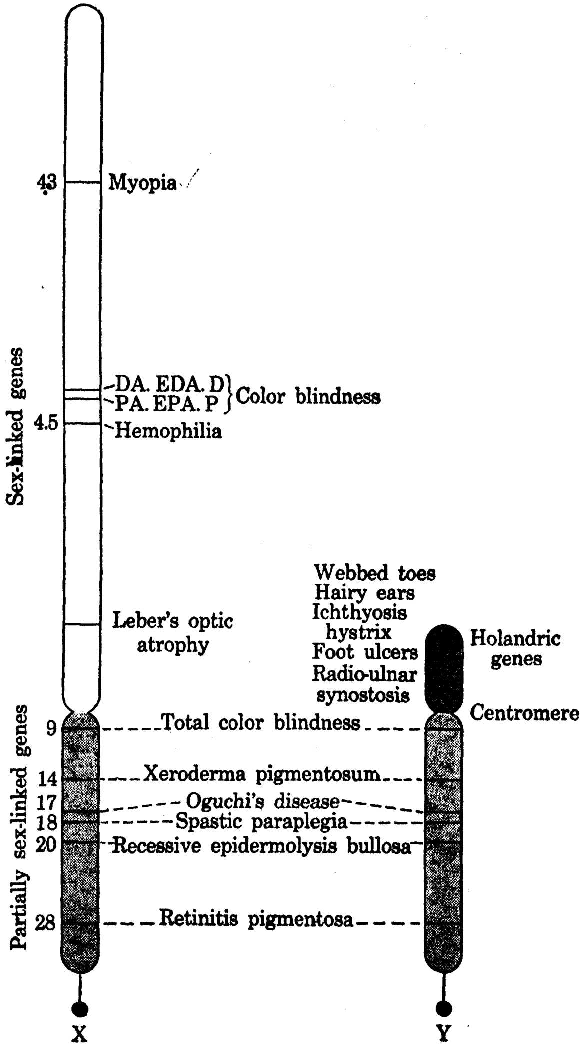

Fig. 23. Diagram of the sex chromosomes and some of their contained genes.

On the basis of present knowledge, a very tentative map of the X- and Y-chromosomes can be drawn up (Fig. 23). As already pointed out, the cross-over values of the genes in the homologous part of the X are very approximate and even the order of some may be changed. In the non-homologous part, it is known that the genes for deuteranopia and protanopia are very near together and the cross-over values between (1) deuteranopia and hemophilia, (2) deuteranopia and myopia, are known, but whether they are on the same or opposite sides of deuteranopia is only a guess. Regarding the many other (thirty or more) sex-linked genes, it is not yet known whether they are partially or wholly sex-linked, so there is no point in trying to locate them at present. Probably the bulk of them are in the non-homologous region, since they have shown no clear evidence of crossing-over. Leber's optic atrophy, however, does show such indications and is probably near the point of contact between these two parts of the X. The gene for epidermolysis bullosa in one pedigree is in the Y with at least one case of cross-over to the X.

We append in Table 4 below (1) a list of genes known to be in the X-chromosome, with an indication of those abnormalities which are

TABLE 4

LIST OF GENES IN X- AND Y-CHROMOSOMES

1. *Genes in the X.*

Color-blindness
Night-blindness 3 *
Leber's optic atrophy 3
Myopia (recessive, irregular dom.)
Megalocornea 3
Coloboma
Nystagmus 3
Microphthalmia 3
Ichthyosis
Hemophilia
Toothlessness
Pseudohypertrophic muscular dystrophy (rec.)
Pelizaeus-Merzbacher brain hypoplasia
Nomadism
Keratosis follicularis spinulosa decalvans
Retinitis pigmentosa 3
Hypoplasia of iris stroma (dom.)
Congenital cataract (Stieren pedigree) 3
Absence of macula with albinism of the eye
Atrophia gyrata choroideae et retinae
Detachment of retina 3
Glaucoma (dom.)
Myopathy (Vermeylen and Minne)
Peroneal atrophy 3
Infantile facio-scapulo-humeral amyotrophy (dom.)
Progressive musc. dystrophy 3
Dipsomania (Kroon)
Lipomata? (dom.)
Sex-linked factor for mental deficiency (Rosanoff)?
Dark brown teeth (dom.)
Deafness (rec.)
Albinism (1 pedigree) 3
White forelock (1 pedigree)
Keratosis follicularis (dom.)
Ichthyosis vulgaris (dom.)
Sebaceous cysts 3
Psoriasis 3
Pityriasis versicolor
Anidrotic ectodermal dysplasia (dom.)
Absent medial incisors
Syringomyelia (foot ulcers) (dom.)
Morquio's disease (1 pedigree)
Thrombopathy
Cylindromata?
Spastic paraplegia

2. *Genes in the Y.*

Ichthyosis hystrix
Black hairs in the ears
Webbed toes
Coloboma iridis (?). Sedgwick's case
Cataract (?). Harman's case
Keratoma dissipatum (3 fams.)

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* This indicates characters which are known to be inherited as dominant, recessive and sex-linked.

Peroneal atrophy, 1 case of cross-over, $X \longrightarrow Y$
Epidermolysis bullosa simplex (Yaffe)
Radio-ulnar synostosis (1 ped.)
Hyperextensibility of thumbs? (1 ped.)
Hypermobility of joints (1 ped.)?
Blue sclera & brittle bones (1 ped.)
Adherent tongue (possible)
Camptodactyly (1 ped.)?

3. *Hologynic inheritance* ($\widehat{XX}$).

Color-blindness (Cunier ped.)
Sebaceous cysts (1 ped.)
Absence of upper lateral incisors? (Schultz ped.)
Distichiasis (leDouble and Houssay ped.)
Cataract (Galezowski's ped.)
Early decay of teeth? (Sedgwick ped.)
Ectopia lentis (Cameron)?

4. *Probable or possible autosomal linkages.*

Ptosis and epicanthus with brown eyes and hair
Color-blindness and a crooked little finger (Macklin)
Myopia and eye color (probable). Burks 10%(?) crossing-over
Myopia and retinitis pigmentosa (Usher, 1935)
Myopia and hemeralopia
Cataract and a sublethal factor (Stieren, 1907)
Cataract and curly hair (Werner, 1928)
Absence of macula and aniridia (Vogt)
Retinitis pigmentosa and deafness
Retinitis pigmentosa and glaucoma (possible)
Glaucoma and dark eyes (possible)
Aniridia and syndactyly (possible)
Brachydactyly and microcornea
Apical dystrophy and macular coloboma (probable)
Arachnodactyly and ectopia lentis (may be one gene)
Cat's ear and ptosis
Otosclerosis and susceptibility to tuberculosis
Otosclerosis and blood groups (Jannuzzi, 1929), probable
Albinism and mental derangement
Blond hair and albinism (possible)
Fair hair, light eyes and piebaldness (Cockayne, 1935)
Monilethrix and dark hair, probable
Ichthyosis vulgaris and allergy, probable
Ichthyosis and imbecility (7 Norwegian families)
Poikiloderma and recessive radial polydactyly, probable
Alopecia areata and dark hair, possible
Dystrophy of hair, nails, and blondness, probable
Leuconychia totalis and epidermoid cysts
Angiokeratoma and dark hair
Absence of incisors, molars, and dark hair (Beadle, 1926)
Opalescent dentine and lamellar cataract and fits, possible
Defective enamel and juvenile cataract, possible
Hypertrophied nails and erupted teeth at birth, possible
Brachymetacarpy and schizophrenia (Miskolczy), possible
Clinodactyly and brunet coloring (Tomescu)
Exostoses and red hair (Weber), possible
Camptodactyly with (1) anonychia pollicum, (2) absence of patella, (3) luxation of head of radius
Eye and hair color with diabetes mellitus, possible
Erythroblastic anaemia and blood groups (Caminopetros)
Hemolytic icterus and blood groups? (Hittmair and Auhuber)
Persistent pupillary membrane and microcytic anaemia? (Hansen and Klein)
Harelip, cleft palate and cleft hand and foot, probable
Periodic paralysis and genes for stature, possible
Myotonia congenita and genes for skin, hair and eye color and nose shape
Myoclony and epilepsy, possible
Finger-print patterns and blood groups (Hesch)
Tylosis palmarum et plantarum and lipomata
Handedness and D pattern in the 4th interdigital area

also autosomal dominant or recessive or both; (2) a list of genes probably or certainly in the Y; (3) probable cases of hologynic inheritance; (4) a number of more or less definite autosomal linkage groups or linked pairs. Some of these may be shown later to belong to one larger linkage group.

The ABO blood groups may be linked with red hair and with Friedreich's ataxia and phenylketonuria. Certain factors for eye, hair and skin color are clearly linked, but the gene for red hair is independent of eye color. Brachydactyly is probably independent of ABO and Tt (taste-blindness). Polydactyly shows no evidence of linkage with the blood groups. Using the recent linkage methods, Kloepfer (1943) investigated the linkage relations of 19 characters, some of them multifactorial and 9 of them not previously used. A study of 223 sibs in 27 families gave presumptive evidence of autosomal linkage in 16 pairs of characters.

LITERATURE

Aida, T. 1930. Further genetical studies of *Aplocheilus latipes*. *Genetics* 15:1–16.

Bell, Julia & Haldane, J. B. S. 1937. The linkage between the genes for colour-blindness and haemophilia in man. *Proc. Roy. Soc.* 123B:119–150.

Bernstein, F. 1931. Zur Grundlegung der Chromosomentheorie der Vererbung beim Menschen mit besonderer Berücksichtigung der Blutgruppen. *Zeits. f. Abst. u. Vererb.* 57:113–138. 1933. 63:181–184.

Bernstein F., Borison, H. L. & Finkel, S. 1943. A case of spurious linkage, as claimed for the classical blood groups and allergy. *J. Immunol.* 46:245–248.

Boyd, W. C. & Boyd, L. G. 1941. Data for testing the genetic linkage on 500 pairs of sibs. *Ann. of Eugen.* 11:1–9.

Burks, Barbara S. 1937. Retinitis pigmentosa tested for incomplete sex linkage. *Eugen. News* 22:33–42.

———. 1938. Autosomal linkage in man — the recombination ratio between congenital tooth deficiency and hair color. *Proc. Nat. Acad. Sci.* 24:512–519.

———. 1941. Autosomal linkage in man. *Proc. Genet. Congr. Edinb.* P. 82.

Castle, W. E. 1940. *Mammalian Genetics.* Harvard University Press. Pp. 169.

Clark, F. H. 1935. Linkage relations of Zavadskaia shaker in the house mouse (*Mus musculus*). *Proc. Nat. Acad. Sci.* 21:247–251.

Cotterman, C. W. 1937a. The detection of sex-linkage in families collected at random. *Ohio J. Sci.* 37:75–81.

———. 1937b. Indication of unit factor inheritance in data comprising but a single generation. *Ohio J. Sci.* 37:127–140.

Davenport, C. B. 1930. Sex linkage in man. *Genetics* 15:401–444.

Finney, D. J. 1939. Tests for sex-linkage in a quantitative character. *Ann. of Eugen.* 9:203–207.

———. 1941a. The detection of linkage. II. Further mating types; scoring of Boyd's data. *Ann. of Eugen.* 11:10–30.

———. 1941b. III. Incomplete parental testing. *Ann. of Eugen.* 11:115–140.

———. 1941c. An apparent linkage of the OAB blood groups with allergic disease. *Proc. Genet. Congr. Edinb.* P. 120.

———. 1942. Detection of linkage. IV. Lack of parental records and the use of empirical estimates of information. *J. Hered.* 33:157–160.

———. 1943. VII. Combination of data from matings of known and unknown phase. *Ann. of Eugen.* 12:31–43.

Fisher, R. A. 1934a. The effect of methods of ascertainment upon the estimation of frequencies. *Ann. of Eugen.* 6:13–25.

———. 1934b. The amount of information supplied by records of families as a function of the linkage in the population sampled. *Ann. of Eugen.* 6:66–70.

———. 1934c. The use of simultaneous estimation in the evaluation of linkage. *Ann. of Eugen.* 6:71–76.

———. 1935a. The detection of linkage with "dominant" abnormalities. *Ann. of Eugen.* 6:187–201.

———. 1935b. The detection of linkage with recessive abnormalities. *Ann. of Eugen.* 6:339–351.

———. 1936a. Heterogeneity of linkage data for Friedreich's ataxia and the spontaneous antigens. *Ann. of Eugen.* 7:17–21.

———. 1936b. Tests of significance applied to Haldane's data on partial sex linkage. *Ann. of Eugen.* 7:87–104.

———. 1939. The precision of the product formula for the estimation of linkage. *Ann. of Eugen.* 9:50–54.

Fortuyn, A. B. D. 1939. The incidence of the various genotypes in a population showing a sex-linked recessive character. *Genetica* 21:434–444.

Haldane, J. B. S. 1934. Methods for the detection of autosomal linkage in man. *Ann. of Eugen.* 6:26–65.

———. 1936. A search for incomplete sex-linkage in man. *Ann. of Eugen.* 7:28–57.

———. 1938. Congenital disease. *Lancet* 235:1449–1454.

———. 1941a. The partial sex-linkage of recessive spastic paraplegia. *J. Genet.* 41:141–147.

———. 1941b. New data on partial sex-linkage in man. *Proc. Genet. Congr. Edinb.* P. 137.

Hesch, M. 1932. Papillarmuster bei Eingeborenen der Loyalty-Inseln. *Zeits. f. Rassenphysiol.* 5:163–168.

Hogben, L. 1932. The correlation of relatives on the supposition of sex-linked transmission. *J. Genet.* 26:417–432.

———. 1934. The detection of linkage of human families. I. Both heterozygous genotypes indeterminate. *Proc. Roy. Soc.* 114B:340–352.

———. II. One heterozygous genotype indeterminate. *Proc. Roy. Soc.* 114B:353–363.

Hogben, L. & Pollack, R. 1935. A contribution to the relation of the gene loci involved in the isoagglutinin reaction, taste blindness, Friedreich's ataxia and major brachydactyly in man. *J. Genet.* 31:353–361.

Hutt, F. B. & Lamoreux, W. F. 1940. Genetics of the fowl. 11. A linkage map for six chromosomes. *J. Hered.* 31:231–235. Figs. 2.

Jannuzzi, S. 1929. Gruppi sanguini ed otosclerosi-ricerche. *Ricerche, Arch. Ital. di Otol.* 40:499–518.

Kloepfer, H. W. 1943. An investigation of 171 possible linkage relationships in man. *Abst. of Doctoral Diss.* Ohio State University Press. Pp. 221–228.

MacArthur, J. W. 1934. Linkage groups in the tomato. *J. Genet.* 29:123–133.

Madlener, M. 1928. Eine Bluterfamilie. *Arch. f. Rass. Ges. Biol.* 20:390–394.

Mather, K. 1938. *The Measurement of Linkage in Heredity.* London & New York.

Mather, K. & Philip, U. 1940. The inheritance of hare lip and cleft palate in man. *Ann. of Eugen.* 10:403–416.

Morgan, T. H. 1926. *The Theory of the Gene.* Yale University Press. Pp. 343.

Munro, T. A., Penrose, L. S. & Taylor, G. L. 1941. A study of the linkage relationship between the genes for phenylketonuria and the ABR allelomorphs in man. *Proc. Genet. Congr. Edinb.* P. 224.

Nielson, E. D. 1940. *J. Hered.* 31:4.

Penrose, L. S. 1935. The detection of autosomal linkage in data which consist of pairs of brothers and sisters of unspecified parentage. *Ann. of Eugen.* 6:133–138.

———. 1938. Genetic linkage in graded human characters. *Ann. of Eugen.* 8:233–237.

Philip, U. 1935. Crossing-over between X- and Y-chromosomes in *Drosophila melanogaster. J. Genet.* 31:341–352.

Punnett, R. C. 1923. Linkage in the sweet pea (*Lathyrus odoratus*). *J. Genet.* 13:101–123. Pl. 1.

Race, R. R., Taylor, G. L. & Vaughan, J. M. 1941. A genetic investigation of acholuric jaundice. *Proc. Genet. Congr. Edinb.* P. 244.

Rath, B. 1938. Rotgrünblindheit in der Calmbacher Blutersippe. Nachweis des Faktorenaustauschs beim Menschen. *Arch. f. Rass. Ges. Biol.* 32:397–407.

Riddell, W. J. B. 1937. Haemophilia and colour-blindness occurring in the same family. *Brit. J. Ophthal.* 21:113–116.

———. 1938. A haemophilic and colour-blind pedigree. *J. Genet.* 36:45–51.

Schick, R. 1934. Fünfundzwanzig Jahre Koppelungsuntersuchungen bei *Antirrhinum majus. Naturwiss.* 22:264–266.

Snyder, L. H. 1926. The linkage relations of the blood groups. *Zeits. f. Immunitätsforsch. u. Exp. Therapie* 49:464–480.

———. 1934. Modern analysis of human pedigrees. *Eugen. News* 19:61–69.

Snyder, L. H., Baxter, R. C. & Knisely, A. W. 1941. The linkage relations of the blood groups, the blood types, and taste deficiency to P.T.C. *J. Hered.* 32:22–25.

White, T. 1940. Linkage and crossing-over in the human sex chromosomes. *J. Genet.* 40:403–437.

Wiener, A. S. 1932. Method of measuring linkage in human genetics; with special reference to blood groups. *Genetics* 17:335–350.

Winge, O. 1923. Crossing-over between the X- and the Y-chromosome in *Lebistes*. *J. Genet.* 13:201–217.

———. 1934. The experimental alteration of sex chromosomes into autosomes and *vice versa*, as illustrated by Lebistes. *Compt. Rend. Lab. Carlsberg.* 21:1–49. Col. pls. 2.

Beadle, O. A. 1926. An inherited anomaly of dentition. *J. Genet.* 17 : 199–206. Pl. 1.

Chapter V

EYE COLOR AND HAIR COLOR

EYE color was the first normal Mendelian character recognized in man, when the Davenports (1907) and Hurst (1908) independently suggested that blue eyes are recessive to brown. The Davenport results were based upon a questionnaire to school principals. Hurst examined with a hand lens the eye color of the population of an English village and classified eyes as duplex or simplex, according to the presence or absence of brown pigment on the anterior surface of the iris. It was soon recognized, however, that these distinctions were not sharp and simple, and on the fluctuating conditions observed was based a denial of the existence of Mendelian segregation (Galloway, 1912), which nevertheless undoubtedly occurs. Subsequent studies have greatly extended our knowledge of human eye color and its inheritance. The blue color of the iris is well known to arise from the presence of fine particles scattered in the stroma, by which the light is reflected, the iris thus appearing blue for the same physical reason that the sky is blue. The reflections from a blue dress intensify the blue color of a lady's eyes. When the iris is unpigmented, and relatively transparent, the retinal pigment may rarely show through to some extent.

It was recognized from the first that blue and brown are the two ends of a color series in which increasing amounts of yellow or brown pigment are present in the iris. Galton (1889), in classifying eye colors, used eight categories: 1, light; 2, blue, dark blue; 3, green, blue-green; 4, dark gray, hazel; 5, light brown; 6, brown; 7, dark brown; 8, black. It is still uncertain whether the intermediate shades are due entirely to different densities of the brown melanin pigment, but this seems probable. "Hazel" and "green" eyes are popular terms. These conditions appear to result from different densities of scattered yellow or brown melanin with a more or less blue background.

Since then has come recognition of pattern differences. Hurst (1912) defined three patterns of pigment distribution in the pigmented iris:

self-colored, in which the brown is distributed all the way to the periphery of the iris; ringed, in which the brown is confined to a ring around the pupil; and spotted, in which irregular spots and patches of pigment occur on the blue background. The iris is blue or light gray in the absence of melanin pigment, and this is simply the apparent color of muscle fibres in the iris as seen through the cornea. The stroma or outer layer (connective tissue) of the iris is of mesenchymatous origin and lies in front of the ectodermal layer of the iris. In complete albinos it is devoid of pigment and hence red from the blood vessels.

Riddell (1942), after surveying previous attempts to record eye colors, has developed a new classification involving multiple categories. Eyes were coded according to (*a*) general color, (*b*) presence or absence of diffuse color, (*c*) presence or absence of spots or little masses of color. The general colors were recorded as *blue*, *gray*, *green*, *yellow*, *tan* and *chocolate*, represented by the numerals 1–6. Thus 240 represents a gray eye with some diffuse yellow and no spots. A hazel eye might be 356, i.e., green with diffuse tan color and chocolate spots. There are thus 294 possible categories of eye color, but many of them do not occur. Martin's eye color scale was coded by this method, and 65 classes were required for tabulating the eyes of 500 individuals. Of these, 21 classes were represented by a single case and 4 classes by only two cases. It was found that certain color categories were more frequent in one sex. Thus gray with diffuse yellow (240) was present in 14♂ to 37♀ persons, and tan with diffuse green (530) in 13♂ to 9♀.

By recording the ages of the men and women examined, evidence was obtained that eye colors change regularly during adult life, and earlier in women than men, women of age A having eye colors equivalent to those of men at age A + 29.3 years. The eye colors of young women thus correspond with those of old men. There is also evidence that the large classes of pure blue and gray eyes do not change with age. They probably represent distinct genotypes. On the other hand, eyes which are chocolate in early life may appear green or gray with diffuse yellow or tan and chocolate spots in later years. In many chocolate eyes the contraction furrows (see p. 105) appeared as green lines under higher magnification. It is to be hoped that this new method of classifying eye colors will be tested on a large scale in families, as it offers a further approach to genetic analysis of eye color. Riddell (1943) has since tabulated the eye colors of 500 more persons, the combined data giving a sex difference of 14.4 years. Wessely (1932) also showed that spotted and striped iris can be inherited. Brues

(1939) applied the sib-pair method of analysis to 300 sibs in 83 families, recognizing a background color of the iris and a detail color or pattern. Classifying eyes as light, pale mixed, mixed and dark, she found clear evidence of a sex-linked factor, **M,** making the iris non-light (intermediate), its recessive allele, **m,** producing a light eye. She also deduced a factor, **B,** of unknown dominance making a mixed (variegated) eye brown, and an independent non-sex-linked gene for dark eyes. Hughes (1944), in a statistical study of brown eyes in 107 families with 212 children, finds evidence of multiple factors for degree of brown pigmentation.

Usher (1920), from a careful histological examination of six albino eyeballs, found traces of pigment in four. He therefore concluded that total absence of pigment cannot be used as a definition of albinism in man. The *fovea centralis* [1] in albinotic eyes is shown to be absent or imperfect, and this may be the chief cause of the imperfect vision in such eyes. In the eyes of albinotic individuals belonging to dark races the mesoblastic pigment appears earlier and is found in much larger quantity at time of birth than in European eyes. Chemical examination indicates that there is more pigment in the eyes of albinos of dark races than of white races. This is in accord with much evidence from mammals of a close relation between density of coat color and of eye pigmentation.

A general study of the iris in vertebrate animals, by Ida Mann (1931), serves to place the subject of human iris color in wider perspective. From an extensive study she finds four factors concerned in vertebrate iris color; two are anatomical (the distribution of blood vessels and the shape of the pupil), two optical (the nature of the pigment and the degree of translucency of the tissue). The anatomical conditions are very constant in man, while the pigmentation conditions (unlike those in most wild species) are extremely variable, at least in Caucasian peoples and some others. On the other hand, American Indians, Eskimos, Chinese and Negroes, for example, generally have densely brown or black eyes with relatively little variation in pigmentation.

In the human iris, as expected according to the laws of embryology, the least variable characters are the first to appear in development. Blood vessels are present in the superficial layer of the iris at the eighth week of foetal life, when there are no ciliary processes, no uveal pigment on the back of the iris, no sphincter or dilator muscle and no true pupil. Even at birth, as is well known, there is no mesodermal pigment in the stroma in European babies. The different groups of vertebrates show an extreme variety of eye structure, but throughout the mammals some shade of brown is typical for the iris. This greatly strengthens the view that brown was the original iris color in man.

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[1] This is a pit in the middle of the macula lutea or point of clearest vision at the center of the retina.

Galloway (1912) and others have regarded the yellow pigment of the human iris as simply a dilution of the brown. Davenport (1927) regards it as a different pigment, the same as in a yellow Mongol skin, giving a green eye when uniformly distributed. The biochemistry of melanin pigment is still insufficiently known for a final settlement of this point.

A rare eye color, ruby, has been studied in man by Iljin (1926), who observed it six times in Russia and found that it could occur with either a fair or dark complexion. This eye color is also known in the guinea pig, mouse, rat, cat, dog and rabbit. Roberts (1945) has found it in Hampshire swine.

The color of the human iris undergoes slow changes throughout life. In babies of the white race the eyes are at first dark blue. They may gradually become pigmented or may change to lighter blue, reaching their definitive color in some cases at about six to eight years of age. The state of health also affects the pigmentation, and in old persons the brown iris may develop a peripheral ring of blue through absorption of brown pigment (arcus senilis). American Indian babies of pure blood never have blue eyes. Both hair and eyes are intensely black from birth. I believe this is due to the presence of intensifying factors for eye and hair color. The intensifier for eye color is never present in Europeans and the intense black hair of an Indian baby is rarely, if ever, present in a Caucasian baby. According to Segi, the iris of a Japanese foetus is already pigmented by the fourth month.

Evidence is accumulating that the blue eye has originated more than once as a mutation from the original brown. The condition has spread presumably through repeated mutations. It reaches a high frequency in the Nordic peoples and a gray eye is equally characteristic of the East Baltic race. Blue eyes are also found (Jochelson, 1928) in certain northern Asiatic peoples, where the blue iris appears to have been of ancient origin and among the Berbers of North Africa, an important center for blue eyes.

More surprising is it to find blue eyes among tropical people with dark skins. Davy (1861) cites some interesting observations in southwestern Ceylon which may be quoted in this connection. Between the years 1816 and 1820 he noted five "albinos." He notes that the native skin color ranges from light brown to black, while the hair color varies less than the skin color. Black hair and eyes are most common, and hazel eyes are less uncommon than brown hair. Gray eyes and red hair are still more uncommon, and the light blue or red eye of the albino rarest of all. The five albinos observed were all the children of dark parents. Two were brother and sister and there were two more albinos in this family who had died young. Their skin was very white, eyes "of a very light colour," pupil light flesh color, iris nearly the same but lighter; hair, eyebrows and eyelashes light cream-color. They were evidently slightly photophobic. In another family a young girl, the only child of black parents, had yellowish-brown hair, black pupils and blue iris, and apparently a white skin. He says she would be considered very fair in England. He thus extended the term *albino* to include those with blue eyes and fair hair. The third family consisted of seven children, four dark like their parents, and three "albinos." Two of these had "fair" skin, yellowish-brown hair, large eyes with black pupils, iris bluish-gray, its outer margin hazel. A younger sister, five years old, had dilated, flesh-colored pupils and bluish-gray irides. The author could learn of no descendants having similar characters, but he quotes the opinion of Singhalese savants that the white races are sprung from this albino type "and *ab origine* were merely an accidental variety," which is not very far from the modern point of view as regards these characters. These albinos as a group had a white skin varying in whiteness, hair ranging from light cream-color to yellowish-brown and eye color from blue to more or less pink.

There are other scattered records of blue-eyed Singhalese families, including a recent one from my own observations (Gates, 1938). In these cases there is full coloring of skin and hair, the only departure from normal being the blue eyes. I observed a guide to the temple at Kandy, Ceylon, who had full dark skin color and black, wavy hair with blue eyes. His mother, maternal grandmother, one sister and a young son were in the same condition (see pedigree, Fig. 24). He knew of similar blue eyes in two other families unrelated to his own. The blue eyes, always recessive in other countries so far as known, appear here to be inherited as a dominant character. It can hardly be supposed that the gene for blue eyes is so widespread in Ceylon that the three spouses in this pedigree were all heterozygous for it, although that possibility is not excluded. Genetically it seems probable that there is some relation between the complete albinos and those with fair skin, yellowish-brown hair and blue eyes of the early records on the one hand, and the modern presence of blue eyes only on the other hand. Further research on the Singhalese population would probably throw light on the problem and might even explain how the change from recessive to dominant blue eyes has taken place. Fisher's theory of selection of modifiers does not appear to be applicable. Complete albinism is regarded as a single recessive mutation affecting skin, hair and eye color, and is well known to occur in all races (see Chap. IX). Possibly the gene for albinism in the dark-skinned races has been fractionated while in the persistently heterozygous condition, thus producing types with partially depigmented hair or with blue rather than pink eyes combined with dark hair and skin. Selection would certainly favor the darker-skinned types in the tropics and might thus result in strains with a dark skin and blue eyes. Since dominant as well as recessive albinos are now known (Chap. IX) in different races, it is not surprising that the same is true of blue eyes.

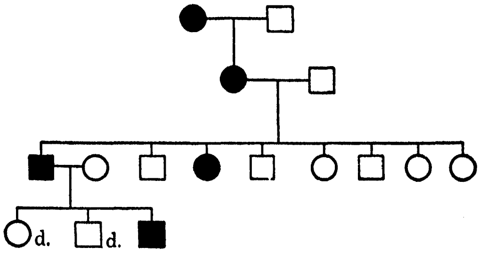

Fig. 24. Pedigree of blue eyes in a Singhalese family.

Although everyone knows that the hair and eyes of children frequently darken as they grow older, yet very little attention has been paid to this developmental aspect of human genetics. It has been shown by Ford and Huxley (1927) that the various eye-color mutations of *Gammarus chevreuxi* depend on genes which affect either the rate of pigment deposition or the time of onset of eye pigmentation. The normal eye is black, melanin deposition taking place two days before hatching. In the red-eyed (**rr**) mutant the time of onset is later and the rate of deposition is slower. One modifier (**s**) slows down the rate of deposition, another (**m**) retards it less. In the type with genetic composition, **rrSSMM,** at 23° C. the eyes begin to darken in four to six days after hatching and become a deep chocolate in three weeks. In the type **rrssMM** they begin to darken in four to eight days and reach equilibrium at light chocolate in five to seven weeks. Another gene (**d**) delays pigmentation of the eyes until sexual maturity.

The genes controlling the changes in eye color in man are unlikely to be less complicated in their action, and an analysis of the developmental aspect as regards both eye color and hair color is of fundamental importance. Godin (1933) has made detailed observations on the changes in eye color of one hundred French boys during puberty. He recognizes that the inner and outer zones of the iris are distinct and change independently. At the beginning of puberty brown eyes show a "clearing up" of their original color in both sexes. The changes are more numerous in adolescents with clear eyes and late puberty, rays, spots and stipples arising on the basal color in both zones, the striae and spots in the outer zone foretelling the future color of the inner zone. At the ages thirteen to eighteen there was a marked color change in four cases.

In one boy with puberty at 17, the outer zone was clear gray at 13½, the inner zone with clear brown rays on a gray background; at 15 the outer zone was dark brown, the inner clear brown; at 15½ the brown was very clear; at 16 the outer zone was dark gray, the inner zone brown. In another boy with puberty at 17½ the iris was gray with yellow streaks at 13½, at 14 the outer zone was gray, inner zone greenish; at 15 greenish-blue; at 15½ greenish; at 16 clear gray, at 17 blue, at 17½ brown. In one case the outer zone changed from blue to gray without the inner zone ceasing to be brown. There is thus no regularity in the eye-color changes during this period, but the eye color is stabilized at the end of puberty, about two years after its beginning. It is probable that in some of these cases eye-color changes had begun before thirteen, and in many children the change from blue to brown occurs at a much earlier age.

MacConaill has had the merit of attacking the subject from the genetical point of view. MacConaill and Ralphs (1936) made observations on 2670 males in Sheffield between the ages of five and twenty-one years, grouped according to age. They find that only dark blue eyes and light blond hair show a steady fall in percentage frequency over the whole period. The adult population of Sheffield contains 21 per cent pure blonds, 21 per cent pure brunets and 58 per cent mixed types. They find that eye and hair color may continue to darken up to the completion of adolescence.

Those with dark blue eyes and light blond hair are called *leucochrome*. This coloration is typical of infancy. The percentage of leucochromes at any age in the Sheffield population follows an exponential curve of decrease to the fourteenth year, after which it has a constant value of 17 per 1000. This is the recessive type in inheritance and from it are derived all the other types in a developmental sense. It thus represents an infantile or paedomorphic condition. The *brunets* have brown eyes and brown or black hair. The mixed class or *heterochromes* include the remainder. The brunets and heterochromes together constitute the *allochromes*. In children who change from leucochrome to brunet the change in hair color and eye color is usually not simultaneous, but one takes place before the other.

In another paper on Sheffield schoolboys, MacConaill (1938a) points out that half the leucochrome children are potential blonds, i.e., they will retain blue eyes and fair hair. Two-thirds of the other half will become brunets. About one-quarter of the leucochromes change each year into other types. By the beginning of the school period (five years?) all but 4 per cent of the adult number of heterochromes have been formed. At this time also two-thirds of the adult number of blonds and six-sevenths of the adult number of brunets are present.

By comparison with the Sheffield population, a study was made of the island of Rachrai off the coast of northern Ireland, whose people have a tradition of Scandinavian ancestry mixed with an Irish element. They form a typical Nordic group with more red hair and less dark hair and eyes than Sheffield. Twenty-five per cent of the men of Rachrai are pure blond, having dark blond hair; 90 per cent have blue eyes, and those with dark eyes had parents who came from outside the island.

In a later study (MacConaill, 1941), the classification of eye color and hair color is placed on a more definite genetic basis. Eyes are classed as blue or dark, the dark including gray. Hair is classed as blond or dark, the latter including red hair. Persons with brown eyes and blond hair are *cyanopic*, those with blue eyes and dark hair are called *glaucopic*. The latter type are found to reach a stable state in the population at the beginning of the second quarter of the post-natal period, which would be at about six years. The cyanopes are most numerous in the second quarter of the post-natal period, blonds being (developmentally considered) residual. The percentage of blonds ranges from 27.4 in the Isle of Man, which was under Norse dominion in the ninth century, to 21 to 24.4 per cent in Sheffield. Thus roughly one-quarter of the population are of blond type. It is concluded that if eye color and hair color were independent this figure would be only 15 to 16 per cent. Much other evidence, some of it from race crossing and some unpublished, goes to show that the genes for eye color and hair color lie at different loci of the same chromosome.

There are found to be nine developmental classes of hair- and eye-color combinations. Following MacConaill, we may assume that **eE** are a pair of factors for blue or non-blue eyes, and **hH** for blond or dark hair. As regards the development of pigmentation in Caucasians, there are then three classes of dark: (1) *fast*, i.e., those who develop full pigmentation soon after birth; (2) *medium*, whose pigmentation is fully developed at puberty; and (3) *slow*, in which full pigmentation of hair and eyes is only reached at about twenty years. On this basis various genotypes may be listed as follows:

EEHH	Fast dark
EEHh	Medium dark with a cyanope stage
EeHH	Medium dark with a glaucope stage
EeHh	Slow dark, with intermediate stage variable
EEhh	Fast cyanope
Eehh	Slow cyanope
eeHH	Fast glaucope
eeHh	Slow glaucope
eehh	Blond

From the original condition **EEHH** we may assume that **E** first mutated to **e** (blue eye) and that this happened independently at least in the European and Singhalese people. Pure brown eyes are found to be scarce in Iran and Iraq, a frequent type being brown around the pupil with blue in the periphery. In this region with a population having Mediterranean affinities, and in parts of Siberia, light-eyed mutations have spread in association with dark hair. The combination of blue eyes with dark hair is characteristic of the people of Ireland and, as already mentioned, it also occurs in Ceylon in association with a black skin. We may assume that in Europe the mutation to blond hair (**h**) came later and that the Nordic and east Baltic types with fair hair and blue or gray eyes are recombination types containing the double recessive. If **e** and **h** originally occurred as independent mutations, crossing-over or recombinations must have taken place later in order to stabilize the blond **eehh** type.

From the developmental point of view **e** and **h** are genes inhibiting the rate of pigmentation. That the population of the British Isles has become markedly blond is shown not only by the high percentage of **eehh** type but by the frequently delayed pigmentation of those who ultimately become dark. On this view the glaucope type in Europe is an earlier condition than the pure blond, and has not been derived from the latter by crossing-over. The glaucope and cyanope types under European conditions were not selected against by the climate, and sexual selection may have acted strongly in their favor, leading finally to multiplication of the double recessive **eehh** blond type of pigmentation, as found in the Nordic and east Baltic races.

Bosshart (1939) has made observations on eye and hair color in two Swiss valleys in the Bernese Oberland, including Adelboden, with an indigenous peasant population. She found that boys and girls had mostly blond hair to the age of fourteen, the men mostly black and the women brown. While 40 per cent of the youths of both sexes had blue eyes and blond hair, 30 per cent of the men and 17 per cent of the women had blue eyes and brown hair. Dark eyes and hair were found in only 2.6 per cent of boys, 4.8 per cent girls, 7 per cent men and 5.2 per cent women. Blue eyes and dark hair thus occurred in *ca.* 47 per cent of the men and (including mixed eyes) 41 per cent of the women. These people were mesocephalic, cephalic index 80.52 (men), 80.70 (women), 36 per cent of the men being brachycephalic. The C. I. is lower than for South Germans, Austrians, French, Italians and all other Swiss. In an early paper on the population of Alsace, Pfitzner (1897) found that females had less blond hair and darker eyes than males. Those with black hair and light eyes, regarded as a special group, numbered 15.9% of the men and only 3.4% of the women.

By comparison, Hägler (1941) studied about eight hundred of the inhabitants of Tavetsch, a high alpine valley in the Bündner Oberland. They were mountain peasants, mostly of Dinaric race. The C. I. 82.9 (men), 83.1 (women) shows brachycephaly. The hair was darker, 71.4 per cent of youths having brown to black hair, only 3.1 per cent of the men having blond or dark blond hair. Two women had red hair. In eye color, men were 21 per cent blue, 34.1 per cent mixed, 44.9 per cent brown; women 12.6 per cent blue, 25.2 per cent mixed, 62.2 per cent brown. A remarkable feature is that the older age groups have lighter eyes. At 7 to 16 years the males had 55.4 per cent, the females 66.3 per cent brown eyes, while at 50 to 60 years the figures were 30.6 per cent and 51 per cent respectively. The nature of this lightening of the eyes, which is more marked in the men than the women, is not clear. It seems to imply pigment absorption in the iris. This paper contains much other anthropological material.

In an elaborate study of the Anatolian Turks, Wagensail (1931) recorded the distribution of eye color and head shape. A strong Nordic element is assumed from the high percentage of light eyes and hair throughout the land, but most strongly represented in the west and south. The small, dolichocephalic heads are derived from the Mediterranean race in the west and south and from the Oriental race in the east. In the middle north, however, where light eyes are most frequent, the heads are short and broad (practically all brachycephalic or hyperbrachycephalic). Hauschild tried to account for this condition by means of his Sarmatian race with blond, broad heads and straight nose (North Slavs). But crossing of this brachycephalic, fair type with the autochthonous brachycephalic, dark race would not account for the excess of light eyes in this region.

Bijlmer (1940), in an anthropological study of the Netherlands, distinguished blue, gray or green and brown eyes as three categories, but recognized transitions. He regarded green as diffuse brown pigment over blue, and gray as a thin, almost yellow layer over blue. Sometimes gray is due to gray bundles of connective tissue in the iris stroma. Among over 3000 persons he found two pairs of yellow eyes. The hair was blond and the yellow seemed a different pigment. The local distribution of eye colors indicates that darker pigmentation and the B blood group have both reached Holland from the sea. There was no correlation between blood group and eye or hair color. Brachycephaly is also commoner in the more pigmented western provinces than in the blond eastern provinces. Its origin is therefore regarded as not Alpine, but problematic.

MacConaill (1938b) developed a formula connecting the proportions of fair hair (**h**), blue eyes (**e**), O (**RR**) blood group and **B** + **AB** blood groups: $\frac{e}{h} = P\frac{B}{RR}$, where P is a parameter defined by the inequality: $1 < P < 3$. He found $P = 2.1$ for Rachrai island and $P = 2.4$ for Sheffield.

In the tropics, it is clear that even given the same initial mutations the racial results would be quite different, because natural selection would act strongly against the complete blond type. This is contrary to the claim of Rodenwaldt (1927) and others that fair complexion is not a disadvantage in the tropics. The glaucope type **eeHH** does not appear, however, to be at any disadvantage, but the white-skinned mutations may well have been suppressed by natural selection.

Before leaving this aspect of the subject, reference may be made to another paper of MacConaill (1938a) in which he studied the stature of male school children in relation to hair and eye color. In a study of 2500 boys, from five to seventeen years old, they were divided into three classes; blond, brunet and heterochrome. It was found that at all ages the mean statures of the blond and brunet groups were greater than those of the heterochrome. The differences in mean stature were statistically significant at all ages except puberty. The blond and especially the brunet groups were also less variable than the heterochrome. A homozygous condition in pigmentation therefore conduces to a better response to the growth hormones, and it may be inferred that the heterochromes are at a selective disadvantage.

The largest pigmentation survey ever undertaken was made by Tocher (1908) on the school children of Scotland. The eye and hair color of 502,155 children throughout Scotland was surveyed. Eye colors were classed as blue, light, medium and dark; hair colors as fair, red, medium and dark or black. Unfortunately eye and hair color were not tabulated together. About 25 per cent of the children were recorded (by their teachers) as fair-haired, 25 per cent dark-haired, 45 per cent brown or medium and 5 per cent red-haired. Tacitus referred to the red-haired Caledonians and excess of red hair is still found in Scotland, but it is uniformly distributed throughout the country. The survey also showed 15 per cent of blue eyes, 30 per cent light, 32 per cent mixed, and 22 per cent dark brown. Dark or jet black hair and blue eyes were associated with the Gallic-speaking population in the western counties. This Scotto-Celt type of coloring is thus similar to the Irish type and doubtless represents one of the earliest strata of the population both in Scotland and Ireland. In his extensive observations of eye and hair color in Britain, Beddoe (1885) found that the Welsh of Upper Galloway were tall with prevailingly blue or gray eyes and dark brown or black hair. He concluded that the primitive Brythons in the district were probably of this type. Hooton (1940), in a preliminary survey of anthropometric results in Ireland, finds that nearly 42 per cent of Irish males have blue eyes and less than 0.5 per cent brown eyes, the association of light eyes with dark hair being "the most striking feature of Irish anthropology."

It is interesting and significant that the genetical and anthropological points of view both lead to the conclusion that this glaucope type is older than the blond type which was brought in by Nordic invaders at a later date.

Tocher found an excess of fair and dark hair in the sparsely populated areas of Scotland and darker eyes in the urban areas. In a discriminant analysis of Tocher's data, Maung (1941) found that the pigmentation index for girls was not significantly higher than for boys. In some European countries it is clear that brown eyes are more frequent in women than men (see below). Urbanization is shown to be associated with darker pigmentation. Some selection seems to be in operation, but it is not clear whether it is due to differential birth rates or selective mortality rates among the various eye-color classes. Tocher's "medium" eyes may be mainly heterozygous, with blue as the recessive. (See Gray, 1907.)

Kollmann (1883) made an earlier survey of 405,609 school children in Switzerland, classing them for eye and hair color. The main results were as follows:

Blue eyes and blond hair	11 per cent
Blue eyes and brown hair	4.4 per cent
Brown eyes and blond hair	13.2 per cent
Blue eyes and brown or black hair	4.5 per cent
Brown eyes and brown or black hair	25.9 per cent

Agreement in hair and eye color was six times as frequent as the reverse.

Skerlj (1930) made a study of eye and hair color in 437 school children seven to seventeen years of age in Ljubljana, Slovenia, where the population belongs mainly to the East Baltic race, with some Dinaric and Alpine elements. He found light eyes 58.7 per cent, dark eyes 41.3 per cent, light hair 51.3 per cent, dark hair 48.6 per cent. More girls than boys had light eyes and light hair, but the evidence from ages shows that the percentage of dark eyes did not increase with age and there was only a little darkening of the hair, especially in the girls. There were more glaucopes (light eyes and dark hair) than cyanopes. It was only these mixed types which changed with age. Martin (1928) found evidence that undernourishment in children of one to four years produced a darkening of the eyes through pigment deposition.

Hesch (1931), in a study of eye color according to age and sex, found in females, brown eyes at age birth to six years in 7.8 per cent; in males of the same ages, 20 per cent. At puberty these numbers were about equal. Rarely the newborn were found to have dark eyes and dark hair which were depigmented later, the dark color at birth being ascribed to a hormone effect from the mother through the placenta. Dark eyes were found to increase in the population from seven years onwards to fifty-six, when depigmentation begins. Increase of pigment in the inner ring is an expression of age-darkening, which is greater in females than in males. Streiff (1932b) made observations on the hair, eye and skin color of 166 children in a Swiss school in Genoa, but without any definite conclusions.

The Chitpavan are a Brahman people on the coast of India between Goa and Bombay. Karvé (1931) examined the eye color of 3097 of all ages. Their eyes were lighter than in the Deccan and the women had darker eyes than the men. Some eyes were green ("cats' eyes"), green-blue or gray-blue, but none blue. Many very young children had black-brown eyes, but there was a marked decrease of this color in the first five years. Another lightening of most eye colors began at *ca.* thirty-five years. About 5 per cent of the population had blue-gray eyes.

Gross (1921) made a study of the relations between eye color and hair color in a German family in which the father had blue eyes and brown hair, the mother blue eyes and blond hair. The eldest daughter had brown eyes and brown hair, two sons and a daughter had blue eyes and blond hair, another son having blue eyes and brown hair. He explains the results by assuming a chromogen factor (P) for iris pigmentation, another (D) for hair pigmentation, and an enzyme factor (F) which activates both. This type of explanation has not been followed in later work. Gross says that in Baden 64.5 per cent of the people are blue-eyed but only 24.3 per cent have blond hair, while in Holland 45 per cent of the brown-eyed are blond.

Staffe (1922) examined the hair and eye color of 3058 boys and 3014 girls between six and fourteen years of age in the Kuhländchen, the original home of Mendel. The boys showed 46.2 per cent light eyes, 20.3 per cent mixed, 29 per cent brown and 4.45 per cent black, and as in Scotland there was clearly no excess of brown eyes in the girls, their eye color distribution being substantially the same.. Probably the excess of brown-eyed women results from girls whose eye color changes from blue to brown after puberty.

Bryn (1920) collected statistics in Norway and states that in four out of thirty marriages two blue-eyed parents had some brown-eyed children. From these four marriages there were ten children with brown eyes and seventeen with blue. One or both grandparents, in all cases, had brown eyes. Winge (1921), in a much more extended study, concludes that such cases are exceedingly rare if the parents have normal vision. By means of a questionnaire, Winge collected data of eye color in about 1400 children of natural history association members in Denmark and their parents. The results are given in Table 5.

From the table it will be seen that, in addition to the seven children with doubtfully blue eyes from blue-eyed parents, twelve children (belonging to eight families) had brown pigment in their eyes. Further information obtained from five of the families indicates that the condition was due in two cases to abnormalities in the eye. In another family of seven, two of the daughters had some brown pigment in their eyes, and one of the latter married a blue-eyed man and had six children, all blue-eyed. This case is thought to be explained by assuming that one of the grandparents was genotypically brown-eyed but had a "pigment restrictive disposition" which made him or her phenotypically (i.e., visibly) blue-eyed. The brown-eyed daughter having blue-eyed children is explained by sex-linked inheritance.

TABLE 5

INHERITANCE OF EYE COLOR IN DENMARK (Winge)

	Number of Children			
Marriages	*Blue*	*Brown*	*Grayish-Green or Bluish-Green*	*Total*
Blue × blue	625	12	7	644
Blue × brown and conversely	317	322	9	648
Brown × brown	25	82	—	107
Total	967	416	16	1399

That there are more brown-eyed women than men was borne out by statistics of 300,000 school children, collected by S. Hansen. Similar results have been obtained by others. Winge shows the fact of sex-linkage by giving the results of marriages in which the parents had different eye color. (Tables 6, 7.)

TABLE 6

MOTHER BLUE × FATHER BROWN

Eye Color of Children	*Sons*	*Daughters*	*Total*
Blue	63	50	113
Brown	65	81	146
Grayish-green or bluish-green	4	2	6
Total	132	133	265

Clearly, when the father has brown eyes, half the sons have blue eyes and half brown, but many more daughters have brown than blue eyes, although the total numbers of the sexes are equal. On the other hand, when the mother has brown eyes there is an excess of blue-eyed sons and daughters. These results are explained by assuming that in addition to the simple pair of factors originally recognized, there is another dominant factor for brown eyes which is sex-linked in inheritance.[2] Winge is further obliged to assume that female germ cells (**bW**) containing the sex-linked factor (**W**) together with the ordinary determiner for blue, cannot exist.

TABLE 7

MOTHER BROWN × FATHER BLUE

Eye Color of Children	*Sons*	*Daughters*	*Total*
Blue	101	103	204
Brown	97	89	176
Grayish-green or bluish-green	—	3	2
Total	198	195	383

Lenz (1921) also assumes sex-linked factors for brown eyes and had previously suggested that the greater frequency of dark hair in European women than men could be explained by assuming that certain factors for dark hair are sex-linked. Lundborg (1920) found marked differences in the percentage of brown eyes in men and women in Sweden, as shown in Table 8 (standard errors added by Lenz).

TABLE 8

BROWN EYES IN MALES AND FEMALES IN SWEDEN

	♂	♀
Swedes	5.2 ± 1.3	11.2 ± 1.9
Finns	6.3 ± 1.3	11.3 ± 1.8
Lapps	34.0 ± 3	49.1 ± 3.4

Lenz adopted the highly doubtful hypothesis that mongoloids have introduced the sex-linked brown factor into Europe and that the excess of brown eyes in females can be used as an index of the amount of Mongolian blood.

The writer in 1922 had the opportunity of examining the eye color of people in Bergen, Norway. Only about one in fifteen would be roughly classed as brown-eyed, but the blues varied continuously from very light to very dark blue, and so through greenish or yellowish shades (due to a small amount of brown pigment) to pale brown, dark brown being rare. Every grade of color appeared to be represented, with a great predominance of the paler shades.

Frets (1925) confirms others in finding that in western Europe there are more females than males with non-blue eyes. But he finds that in Scotland and southeastern Europe (Russia, Bulgaria, etc.) there is no excess of blue-eyed males. The sex-linked gene for brown eyes therefore appears to be confined to certain parts of Europe. Frets finds difficulty in classifying eyes with traces of yellow pigment, and states that parents with such eyes may have children with more, or with orange pigment in the central part of the iris.

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[2] Bullough (1942) shows that in starlings the males differ constantly from the females in having browner (rather than yellowish) iris. There are also sex differences in coloring of the beak and the feathers of breast and throat.

Philipchenko and Liepin (1913) made a study of eye color and hair color based on a questionnaire sent to the literati of Leningrad. Among 488 parents and 738 children, 22 per cent were classified as blue-eyed, 42 per cent gray-eyed (including green), and 35 per cent dark-eyed. Gray is distinguished from blue by the presence of a factor **B**, so that gray eyes might be **BB** or **Bb**. Cases were recorded in which blue × gray and gray × gray gave children with brown eyes, but these were based on statements of the parents and not on critical observation by the investigators. A factor **C** is assumed for "dark" eyes and probably an intensity factor **D** for black eyes. No evidence of a sex-linked factor was found, such as Winge found in western Europe.

Bollag (1927), working with Professor Vogt, made a study of intermediate eye colors in Switzerland. Vogt finds that children of parents with intermediate eye colors (Mischfarben) are often darker, but may be lighter than either parent. Bollag classifies various agencies that may change iris color: (1) A rare form of heterochromic cyclitis, depigmenting the iris of one eye to blue; (2) early trauma, which may change a blue iris to brown; (3) siderosis or deposit of an iron compound from some foreign body or from the blood; (4) heterochromidia due to melanosis or excessive pigment development in one eye (rarest); (5) early paralysis of the sympathetic, lessening pigment deposition in one eye; (6) smaller differences between the eyes may result from variation.

The mixed eye colors are classified as gray-brownish, gray-yellowish, gray, gray-greenish, yellow-greenish, the density of the pigment deposits accounting for the different shades. Martin Rudolf's standard table of colors was used, giving 16 classes between blue and brown, and 84 parents with their 212 children were examined, only families with 4 or more children being studied. In 11 of these families the children's eye color was between that of the parents, in 7 families some children were intermediate and some lighter, while in 24 families the children's eyes ranged from lighter and intermediate to darker. Bryn and Winge both found cases of children with darker eyes than the parents, but Winge explained them as pathological.

Vogt believes that these intermediate colors are not heterozygotes, but represent *nova* whose origin is not explained by crossing, and he assumes the presence of multiple factors which are independent or coupled. In twenty-five crosses between intermediate colors or conditions, only 42.5 per cent of the children are nearly the same as the parents; 32 per cent have darker brown but intermediate eyes, 59 per cent are intermediate like the parents, and 9 per cent are more nearly blue than the parents. It is difficult to say in how far the results may be due to the segregation of subsidiary factors and in how far to non-inherited fluctuations. The chief point emanating from these studies appears to be that the various intermediate eye colors are not heterozygotes of blue and brown but are due to independent factors not yet analyzed.

The important paper of Bryn (1926), in which he examined some three thousand individuals in Norway and depicts thirty-six different eye types found there, is a critical advance on previous work. He recognized eye types with the pigment in rings, clouds and radial stripes, or diffuse over the whole iris, and concluded that there must be three kinds of factors for eye-color pattern: (1) pigment-producing factors; (2) pigment-distributing factors; (3) pigment-concentrating factors. Brown eyes are assumed to have a series of factors (**K**) for pigment and a series of distributing factors, the albino eye lacking all such factors. **A** and **B** are the pigment-distributing factors, **a** and **b** giving pigment-concentration. Bryn finds that when the parents have a ring, radial or cloud pattern, most of the children will have the same pattern. **A** is assumed to distribute the pigment over the whole iris, and **B** to be weaker, leading to a cloudy effect. Hence two blue-eyed heterozygotic parents may have children with intermediate eyes.

Bryn agrees with earlier writers that no normal eye is devoid of pigment, even blue eyes always having a little yellow-brown pigment. There is therefore a variety of types of mixed eye colors, the differences being both quantitative and qualitative (in manner of concentration). Green eyes usually have a denser stroma and a little hidden brown pigment. It is also concluded that gray eyes are inherited differently from blue, the children of gray-eyed parents having a much greater chance of brown pigment in their eyes than the children of blue-eyed parents.

Many of the shades of blue found in Scandinavian eyes are paler than the blue eyes usually found in more southerly populations. The inheritance of these smaller differences in eye color can perhaps be analyzed only with the help of twin studies.

Sedgwick (1861) described a family in County Wexford, Ireland, with tortoiseshell-colored eyes. The third generation, numbering sixteen sons and five daughters, are said to have all had the peculiarity, inherited from their mother. The character was probably a simple dominant.

In the detailed study of eye-color inheritance, attempts have been made to overcome the difficulties of classification resulting from the fact that the phenotypic color series extends continuously from pale blue to brown and black, by constructing a series of glass eyes corresponding to the various colors and patterns. One of these is Martin's Augenfarbentafel, in which numbers 4–8 rank as brown, 8–12 as gray or hazel, and 12–16 as blue. More recently, Saller (1931) has described a new eye-color series, with a colored plate showing forty types of iris, from dense brown to light blue. Steggerda (1930) used this method to study eye-color inheritance in families of Dutch descent with mostly blue eyes. In seven families in which both parents had blue eyes twenty-seven children had blue and one had gray eyes. In four families the parents were blue X gray, twelve children having blue and three gray eyes. Three families blue X brown had four children with blue, two with gray and five with brown eyes. A family with brown-eyed parents had three children with brown, one with blue and one with gray eyes. Davenport (1927) expressed the view that blue is recessive to gray and gray to brown, but the relation of blue eyes to gray still requires further elucidation.

Fleischhacker (1936), in a study of eye color in 103 families, found that heterozygotes of blue and brown could have green or green-brown eyes. He found that the structure of the iris affects the color and that there are quantitative sub-genes for iris color.

Iris Structure

More recently, much more detailed studies have been made of the structure and pattern of the iris stroma. Eskelund (1938) has made a notable investigation and detailed study of human iris structure. In cross-section the iris is in four layers: (1) the frontal boundary layer on the upper surface. Under this lies (2) the vascular layer, containing blood vessels and the sphincter (circular) muscle which contracts the pupil. These two layers are mesodermal in origin and contain the pigment which gives the iris its color when present. (3) The third or posterior boundary layer contains the dilator muscle, consisting of radial muscle fibers which dilate the pupil when they contract. (4) A layer of pigmented epithelium. Layers 3 and 4 are ectodermal in origin. They form the opaque posterior wall of the iris and the radial spindle-shaped cells are partly pigmented, as well as the epithelium.

In a surface view of the iris (see Fig. 25), it is divided into an inner and an outer zone, the line between them being quite irregular and more or less zigzag. This irregular line represents the margin of the frontal boundary layer of the iris, which has atrophied in the inner zone around the pupil during development. The appearance of the outer zone depends on the density and pigmentation of this layer. The clearer this layer, the more can be seen of the vascular layer behind it. In deeply pigmented eyes it is quite opaque. The outer zone generally contains from one to six more or less concentric contraction furrows (Fig. 26), the number being the same for both eyes of an individual. This layer also contains a number of wider or narrower crypts or deficiencies, which give the iris its characteristic appearance and form a definite pattern in the eyes of each individual. Both eyes are of the same type not only as regards its crypts and furrows but also in the amount and distribution of the pigment. In no two persons do the eyes agree in all these particulars. The iris pattern is thus comparable with the finger-prints in delicacy as a means of identification.

The human iris is 10.5 to 12 mm. in diameter and the inner zone may be broad or narrow but always has a more or less irregular margin resulting from the process of atrophy. The two zones frequently show differences in pigmentation.

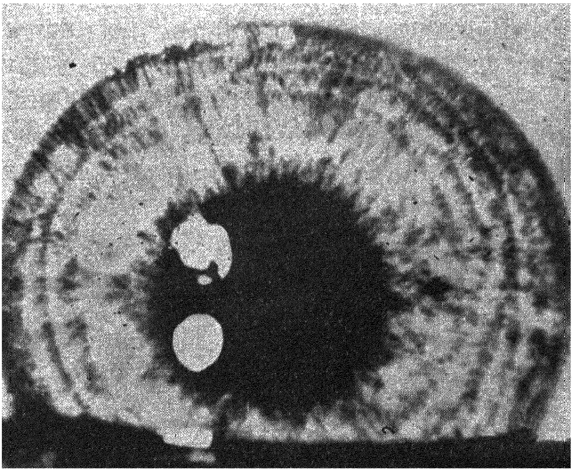


Fig. 25. Photograph of iris, showing narrow inner and wider outer zone surrounding the pupil. Also crypts in outer zone. (After Eskelund)

Eskelund studied the eyes of fifteen couples and their forty-four children. The iris pattern and the number of contraction furrows of the children were found generally to resemble that of one of the parents, but one child had more pigment than either parent. Monozygotic twins were found to be identical in iris patterns. Eskelund divided eye colors into seven types, based on characters of the inner and outer zones. Thus these stroma patterns appear to be inherited, though the laws they follow are as yet unknown.

A study of the iris of similar character has been made by Freerksen (1938). He examined the irides of nine pairs of MZ and eleven pairs of DZ twins, six of the latter pairs being of different sex. His methods were similar to those of Eskelund. In the MZ pairs the structures were always nearly identical and even the lacunae show similarities, whereas in DZ twins, although they are occasionally very similar, the differences in structure of the stroma show that they are not monozygotic. Like Eskelund, he finds that in families some children generally resemble one parent and some the other in iris structure, whereas others are unlike either parent. For instance, contraction rings can be found in the children when they are not present in either parent. Frequently, the iris structure of each parent is repeated in some of the children, but iris pattern appears to be inherited independently of iris color. Freerksen finds a relation between iris structure and body type.

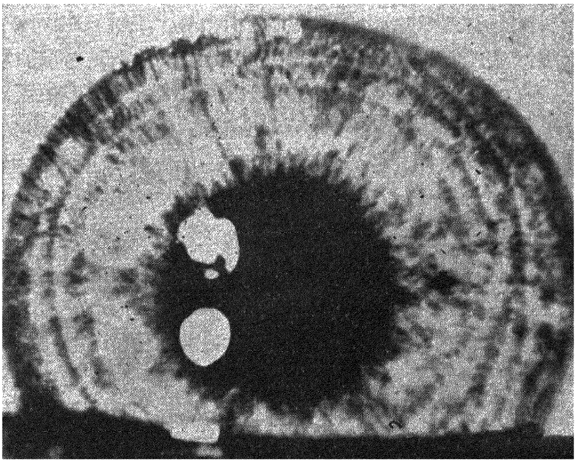


Fig. 26. Photograph of iris showing several contraction furrows. (After Eskelund)

Schwägerle (1938) has made a similar study of iris structure in twins. In thirty-six of the forty pairs examined they could be diagnosed with certainty as MZ or DZ. In four pairs the diagnosis was approached but not certain. The uncertain ones are the strongly pigmented eyes, in which the iris structure is relatively obscure, whereas in light eyes a certain diagnosis is always possible. Iris structure in experienced hands apparently takes first place in the determination of twins. Naevi (chestnut brown flecks) in the iris are considered by him to be of no hereditary value. The study of stroma structure is thus not only of prime importance in twin diagnosis but it opens new lines of investigation in the comparison of parents and children. Brues (1939) made detailed observations of the iris structure in Boston families. She found "specks" (= naevi) comparatively rare. The hereditary type was independent of eye color, but she also found a non-hereditary type which was commoner in women, and associated with mixed eye colors. As the anterior layer of the iris is always at least as highly pigmented as the posterior layer, there is some concomitance between structure and color of the iris. Evidence was found for a dominant sex-linked factor, **C**, which accentuates the atrophy of the anterior layer. The zoned pigmentation was inherited in families, but not as a single factor condition. Many other observations were made.

The detailed study of eye color in twins and their parents is probably essential for a genetical analysis of human eye-color inheritance. That the results till now are far from unanimous or conclusive is shown by the work of Frets (1931, 1932, 1935). He emphasizes the yellow iris as distinct from the brown, and postulates two pairs of non-allelomorphic factors, **A** for brown and **B** for yellow. Blue eyes are then **aabb**. From the examination of numerous families in Holland he finds that truly blue eyes wholly devoid of yellow pigment do exist, but they are rare. Generally a small amount of yellow can be observed around the pupil. Frets examined 5334 persons (2349 ♂ 2985 ♀). Like previous workers, he finds an excess of brown-eyed women. (The women constituted 56 per cent of the whole number examined, but 64 per cent of the brown-eyed were women.) He therefore assumes that the **Aa** pair of genes are in some sense sex-linked, but this assumption is not utilized further in his hypothesis.

In Frets' scheme, yellow and yellowish eyes will be **aaBB** and **aaBb**, while brown and brownish eyes are **AABB, AaBb, AAbb** or **Aabb**. In the cross of brown × blue, if the brown is doubly heterozygous, **AaBb** × **aabb** = **AaBb** + **Aabb** + **aaBb** + **aabb**. This cross should therefore give two children with brown eyes to one with yellow and one with blue. As Frets finds families in which one parent has brown or brownish eyes and the other blue, where the children have brown, yellow and blue eyes, this would exclude the allelomorphism of the genes for brown and yellow. He finds clear segregation, brown × brown producing brown and yellow; brown × yellow producing children with brown, yellow and occasionally blue eyes. But he also records hereditary variations in the tints of brown and yellow. If the pure blue are united with the yellowish eyes, as was evidently done in the early work, then monohybrid ratios show up for the various crosses. Both brown and yellow are in general dominant to blue, and brown is epistatic to yellow. But a number of cases were found where the parents have slight pigmentation of the iris while some of the children have considerably more. Frets (1931) assumed two factors, $\mathbf{B_1}$ and $\mathbf{B_2}$, producing different degrees of brown. $\mathbf{B_1b_1b_2b_2}$ might give a blue eye to superficial observation. If the other parent were $\mathbf{b_1b_1b_2B_2}$, then some children would have brownish eyes ($\mathbf{B_1b_1B_2b_2}$).

It is clear that in the study of eye-color inheritance much turns upon the interpretation of eyes with a small amount of yellow pigment. There must be some fluctuation, but whether its limits are wide or narrow is at present unknown. These limits can only be learned by the study of identical twins. If the conclusion of Schwägerle (1938) is correct that chestnut brown flecks in the iris are of no genetic significance, this will have a bearing on the interpretation of some yellowish eyes. There is much need for further work in this field.

Heterochromia iridis

In this condition, which was known to Aristotle, the two eyes are of different colors, generally one blue and the other more or less brown. It is sometimes associated with diseased conditions such as glaucoma or cataract, the lighter eye being the one usually affected, so that the condition is generally one of depigmentation. Frequently, however, no diseased condition is present. Inherited heterochromia is rare in man, but a number of pedigrees have been published. Gossage (1908) describes a family with nine cases in five generations. One eye, always the left, was grayish blue with chestnut-brown patches. Bond (1912) describes four families of two or three generations in which heterochromia was present. He found a ray pattern of frequent occurrence, with pigmentation only in one or more sectors of the iris of one eye.

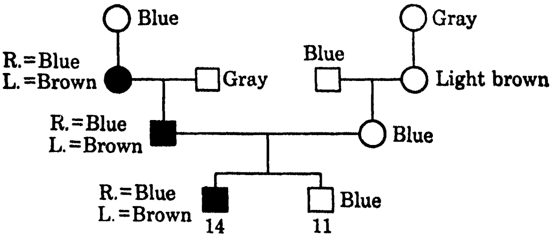


Fig. 27. Inheritance of heterochromidia iridis. (After Nowak)

He estimated that the two eyes are unlike in perhaps one or two individuals per thousand and made many other observations on the subject. In one family the father's left eye was brown with a wide blue ray, the right eye yellow with a ring pattern. The mother had blue eyes. Of the ten children, one daughter had eyes like her father, a son had the same but reversed, i.e., left eye yellow, right with a blue ray. Another son had yellow (ring pattern) eyes and the remaining seven children were blue-eyed like the mother. Nowak (1932) records heterochromia in three generations of a family. In each case the right iris was blue and the left brown. The other eye colors are given in Fig. 27.

Fantham (1926) records a family of English descent with seven cases (all male) of heterochromia in four generations. The original ancestor had one brown and one gray eye. His wife had blue eyes, and of their seven children, three had brown eyes, two blue, one gray, and one son had the same eyes as his father. The eyelashes of the latter were very light brown. He married a blue-eyed woman and of their five children two had brown eyes, two hazel and one son (J. A.) had one brown eye and one gray with white eyelashes. In one of the brown-eyed sons (P. A.) the eyes were of different tints. The children of J. A. were: a son with one brown and one gray eye, lashes brown; a son with one light brown (hazel) and one gray eye, the latter having white lashes; and a daughter with light brown eyes, the left having practically white lower lashes. This is the only indication of depigmentation in a female member of the family. P. A. had two sons, one with brown eyes, the other with one brown and one dark-gray eye. The heterochromia in this family was dominant with a special predilection for the male sex, only one of the six female sibs showing a hint of the character.

Calhoun (1919) describes five cases in a family in three generations, the right eye being light in all. The four affected men also had ptosis in the right eye. In Passow's (1932) pedigree, *a yellow sector in the left eye* (the eyes being otherwise greenish) is present in five persons in four generations. Calhoun cites a case in which the father and mother were blond with blue eyes. The baby had a drooping upper right eyelid, that eye being lighter in color than the other. Seven years later there was evidence of facial atrophy on the right side, the right iris being blue while the left was brown. He concludes that one-sided paralysis of the cervical sympathetic nerve is the cause of the heterochromia and is inherited. Later work has served to substantiate his conclusion that the sympathetic nervous system is concerned in heterochromia.

Several other cases of heterochromia may be cited here. Allan (1905) describes a man of twenty-four with the right eye brown; the left eye was blue except the upper inner quadrant, which was brown. He also (1906) records a case of a boy of eight whose right eye was blue, the iris of left eye in two colors. The upper inner quadrant was brown, the upper outer quadrant partly brown and partly blue, the rest of the iris blue. The sight was normal. His father and mother both had blue eyes. Five brothers and three sisters had blue eyes, except the eldest brother whose eyes were light brown. Wellington (1906) records a man of forty and an unrelated girl of five with one blue and one brown eye. Souter (1906) observed nine cases of heterochromia in one summer. All had good vision. Five were males and four females. Generally only a sector of one eye was affected, being *darker* than the other eye. As this condition occurred generally in gray eyes it may be a dilution effect. It is evidently much more common than true heterochromia in which the irides differ in color throughout, and it is probably a distinct phenomenon.

A striking case of heterochromia in the third generation is described by Ellis (1931). The pedigree (Fig. 28) shows blue and brown eyes segregating in two families in the second generation. In two exceptional individuals, one in each family, the eyes were green-blue and they were presumably heterozygous for eye color. They married, two of their children had blue eyes while the third (III. 3) had the right eye brown and the left green-blue. This would appear to be a phenomenon of somatic segregation, especially as III. 3 also has a sharply marked patch of black hair 6 in. in diameter on the right side of his scalp, the left side being fair. Vogt (1938) describes a pair of identical male twins, age sixty-seven; in each the right eye was blue, with pigment naevi and a dark border (edge) around the pupil, the left brown with a wide dark brown zone in the sphincter region around the pupil (Fig. 29).

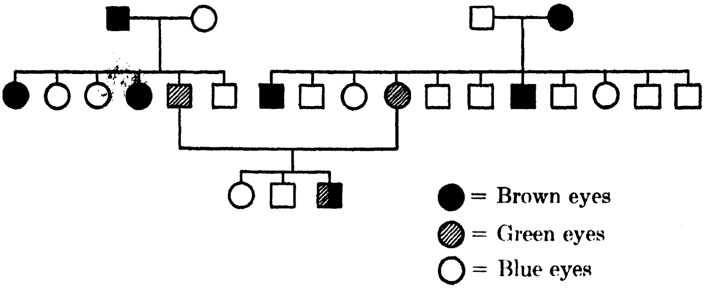


Fig. 28. Origin of heterochromia iridis. (After Ellis)

Heterochromia also occurs in the dark eyes of Japanese. Komai (1934) finds it generally dominant, as in Europeans, but in two pedigrees it is recessive, arising from a cousin marriage.

Three types of heterochromia have been recognized (Streiff, 1932): (1) simplex, (2) involving the sympathetic, (3) Fuchs' type, which is a primary inhibition of pigmentation, not a depigmentation. The second type involves depigmentation of one eye following a lesion of the sympathetic. Kranz (1926) had previously recognized these types. He described ten cases and compared them with the parents. Various other causes of a change in iris color, such as siderosis, unilateral glaucoma or iridocyclitis, were discussed by Streiff (1919). Waardenburg (1932), in a careful study of the subject, says that if heterochromia is in different generations of a family it remains a question whether it is inherited as such, or some other character which acts indirectly to prevent normal iris pigmentation on one side. The partial forms may be caused by insufficient or too strong resorption of the foetal lamina iridopupillaris. Total forms belong either to this category or may be a unilateral change of dominance or the result of an unequal division in development.

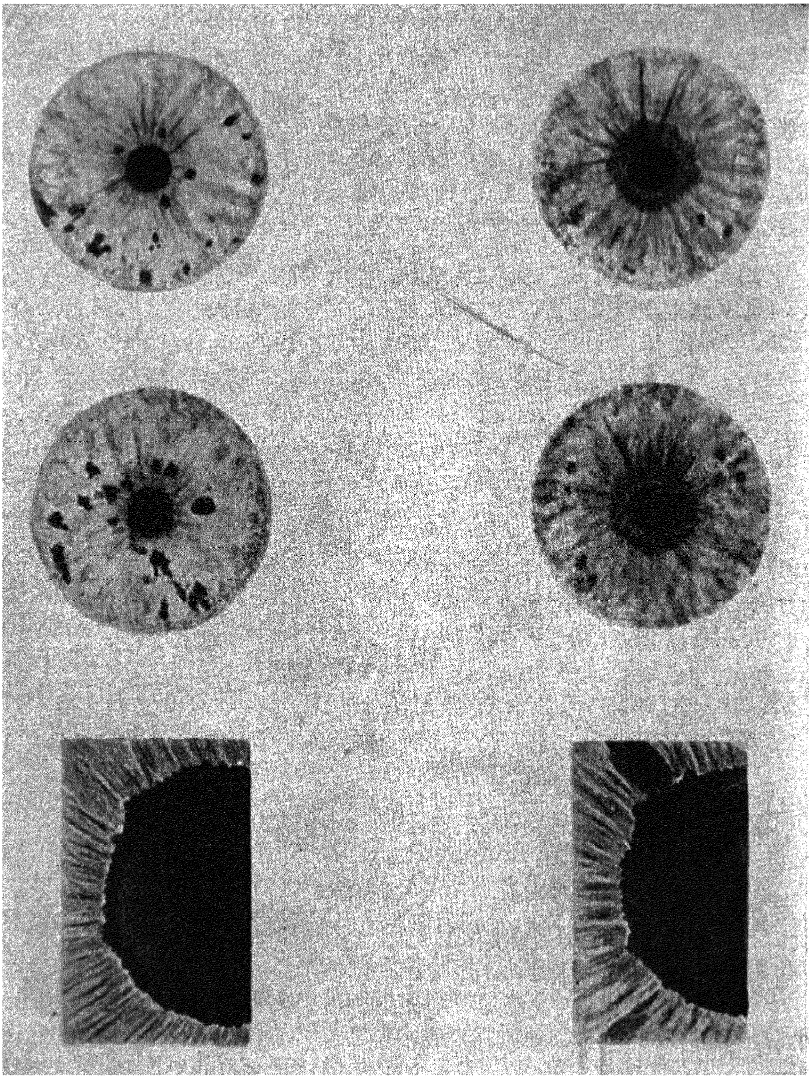


Fig. 29. Right and left eyes of MZ twins with heterochromia iridis. Below is shown the pupil border present in the two right eyes. See text. (After Vogt)

By experiments with animals, Passow (1934) showed that heterochromia iridis follows paralysis of the cervical sympathetic only when the paralysis (cut) occurred before the development of the anterior layer of the iris and its pigment. When a part of the right cervical sympathetic was excised in animals a few days old, they showed homolateral lack of color in the iris later.

Notes on Animal Eye and Hair Colors

Heterochromia is relatively common in rabbits. Punnett (1928) found that the factor **P**, which produces the higher grades of coat pigmentation in the Dutch rabbit, also prevents heterochromidia. Any rabbit without **P** may show the condition. Horses with a "wall" eye are well known, and in various breeds of dogs such as Great Danes, English collies, and Old English sheep dogs heterochromia is not uncommon. In both horses and dogs it is frequently associated with a patchy or piebald coat pattern.

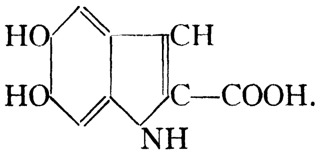
In rabbits the eye-color series is most like that of man and the genetics of eye color in relation to coat color is instructive. Reference may be made to some of the relationships disclosed. Vienna white rabbits have blue eyes, the gene involved being located in a different chromosome from the pink-eyed albino. Dark chinchilla (Sawin, 1932a) has blue eyes while light and pale chinchilla are brown-eyed. Non-agouti dark chinchilla has a black coat and blue eyes. The blue eyes are also affected by several modifiers which produce pigment in the front wall of the iris, giving a gray or mottled eye color. The maximum effect of modifiers is to produce a pseudo-brown. Gray and pseudo-brown eyes are very bluish in the young, but become dark later. The modifiers are independent of the albino series.

In a further paper (Sawin, 1932b) on chinchilla rabbits, it is stated that the order of intensity of the pigment in the choroid and retina is the same as in the coat, and is expressed in the color of the pupil, which ranges from black through brown and blue to pink. The three shades of chinchilla are all alleles of albino and full color. In this graded series coat color and pigmentation of the interior of the eye decrease together. The blue eye of dark chinchilla is either due to the same gene which produces the coat-color or is a mutant gene closely linked with that for coat-color. This condition is quite different from that in man, where the blue-eye factor is independent of skin color, although the range of eye color from blue to brown in chinchilla rabbits is like that in man. Sawin suggests that there are modifiers for iris pigmentation in man as in rabbits, but this remains to be proven.

In a further analysis of hair color and eye color in rabbits, Nachtsheim (1933) assumes five genes, **A, B, C, D, G** for body color. **a** is albino with pink eyes, **b** has no macroscopic visible effect, **c** makes the iris slightly lighter than **C, d** makes the eyes bluish, the intensity depending on the other pigment factors present. Thus **cd** gives the lightest eyes, and **g** has no influence on eye color. All the coat color alleles of the **B** and **G** series have no effect on iris color. The **A** (albino) series, giving a graded series of coat colors to full pigmentation, affects iris color as well, as we have already seen. This series contains six alleles including the chinchillas. Temperature also has an effect on hair pigmentation in this series. We shall have reason to conclude later that in man also certain genes affect both eye and skin color.

The results of histological studies of the hair in various rabbit genotypes may be summarized as follows (Danneel, 1936): The Alaska rabbit, $\frac{\mathbf{ABCDG}}{\mathbf{ABCDG}}$, is distinguished by pigment granules in the hairs which are black, medium size, equally distributed and close together. In other color varieties the granules are variously clumped and distributed. In the Blue Vienna, **ABCdg,** the hairs have larger, looser, black single grains and large clumps (in all **dd** races). Brown Havana, **ABcDg,** differs from Alaska in having *brown* pigment grains. Yellow Thuringian, **AbCDg,** has yellow-brown hair with black tips. All **Ab** races have very small melanin granules and *diffuse* yellow pigment and all wild rabbits have agouti banding (yellow). Gray eyes (**dd** races), with a cloudy, turbid medium on a dark background, have the same physical basis as blue-gray hair color. When pigment granules clump in the hair, the pigment cells (melanophores) clump in the iris.

Saller's theory that the white hair of albinos is a highly oxidized stage in pigmentation, is disposed of by the observation that the black pigment obtained by him by "reduction" of albino hair with stannous chloride is not identical with the natural pigment of black hair. The yellow pigment of **b** and **G** races arises neither from oxidation nor reduction of melanin and has quite a different basic structure. Danneel accepts the results of Raper (1926, 1927) but not those of Saller. The "red pigment" of Raper has been found in an Annelid as an accessory respiration catalyzer. A precursor of melanin, it is probably 5 : 6-dihydroxyindole-2-carboxylic acid. Melanin may be a further oxidation stage,



Many chinchillas, especially the black ones, have mottled eyes due to the reduction of the pigment in the front part of the iris to flecks and spots on a blue background. This may correspond with some of the "hazel" eyes in man, which may therefore represent a dilution effect, although Nachtsheim thinks the mottling of eyes is due to a separate (pattern) factor with no effect on coat color. This mottling effect through dilution, which is only seen in chinchilla rabbits, may be likened to the dilution red spotting seen in the sepals of Oenothera (Gates, 1915) and the petals of cotton (Harland, 1936), after backcrossing to the recessive type. It is quite likely that some of the pigment patterns in the human iris are similar dilution effects.

Dutch-spotting in rabbits is recessive to self-color. The gene affects hair and iris color equally. The extreme minus variation is a rabbit almost entirely white with blue eyes. Animals with somewhat more pigmentation frequently show heterochromia iridis (blue and dark brown, gray and blue, etc.). The eye may be blue with a darker sector or dark with a blue sector. The White Vienna with blue eyes represents a mutation in another chromosome. When these two factors producing blue eyes are united in a heterozygote they behave more or less as a dominant. This change in dominance may be similar to that already mentioned in the blue-eyed Singhalese (p. 92).

The genetics of eye color in cats has certain points of interest in relation to human genetics. Sichel (1847) records that he made observations on white, blue-eyed, deaf cats for over twenty years and always found a correlation between blue eyes and deafness. In one case the iris began to darken at the end of four months and then the kitten first began to hear. Przibram (1908) found that in Angora cats, an animal having one blue and one yellow eye when crossed with a cat having blue eyes or yellow eyes gave some offspring with heterochromidia and some with symmetrical eye color. The color of either eye can be inherited in both eyes of the offspring. The asymmetry could also apparently be reversed, blue (right) yellow (left) producing yellow blue, or vice versa.

Tjebbes (1924) found that in Siamese cats eye color is closely correlated with coat color. In blue eyes there is no tapetum and only minute traces of retinal pigment. In yellowish, gray or brownish gray eyes there is pigment on the outer as well as the inner side of the iris and also usually in the retina and choroid, the tapetum lucidum being a special modification of the front or retinal side of the choroid. Tjebbes also describes a cat with one blue and one yellow eye, the latter eye having a complete tapetum but no retinal pigment.

Bamber (1927) finds that in domestic cats white-spotting is dominant to self color, solid white being dominant to all colors. White cats often have blue eyes and it has long been recognized that such cats are usually deaf. Sometimes one eye is blue and one yellow. In this case the ear on the blue side is generally deaf whereas the ear on the yellow side is normal. This emphasizes the close relation between ear defect and eye depigmentation. Darwin (*Animals and Plants*) suggested that this is due to slight arrest in the development of the nervous system. The eyes of kittens are blue long after they are opened, but these kittens are not deaf; and it is not true that only male blue-eyed cats are deaf. In dogs, the piebald white pattern may invade the inner ear and produce deafness, as in Bull and Fox Terriers (Wright, 1918). In a further study, Bamber (1933) found considerable correlation between blue eyes, dominant white coat and deafness, both in males and females. In how far this is a matter of genetic linkage or of multiple effects of one gene is still unknown.

Staples-Browne (1908) observed that in very young pigeons the iris color is dark, the adult color usually appearing in two months. In the wild rock pigeon, *Columba livia*, and in many domestic varieties the iris is orange, in many other varieties it is white or pearl or red, while in most varieties with white plumage it is black, bull or hazel. In the stock dove (*C. oenas*) the eye is peculiar, its black color being due to the presence of branching cells packed with dark granules in the iris and in deeper tissues.

Many observations on the eye colors of birds and their inheritance are recorded by Bond (1919). His studies were chiefly of pigeons and fowls, although references are made to many other species. The pigment granules producing eye color may be black, brown, yellow, ruby or pearl. The "bull" eye owes its black color, as in the white fantail pigeons, to the absence of pigment from the anterior surface of the iris. The posterior uveal pigment shines through the translucent tissues of the iris and gives the eye its color. The ruddy glow of this eye is due to the plexus of blood vessels. (A similar type of eye occurs in guinea pigs of the type which Castle calls *red-eyed silver agouti.*) But in most birds with dark or black eyes, the color is due to the presence of anterior iris pigment.

In the pearl or white eye of pigeons and the "daw" eye, as in the Malay fowl, there is no anterior pigment in the iris, but its tissues are opaque, owing to the presence of crowded colorless granules. This apparently corresponds with the "wall" eye in horses, dogs and pigs. The muscle fibres of the avian eye, however, are striated or voluntary, and not plain as in the mammals. Pearl eye in pigeons is recessive to yellow or "gravel" eye, as "daw" eye in fowls is to amber or black eye when the latter is due to anterior pigment. The yellow eye derives its color from a network of branching cells containing yellow granules. If the latter are closely packed, the eye may appear black. In fowls the yellow eye may be due to (1) granules in the connective-tissue cells; (2) granules in the striated muscle cells, as in Dorkings and Orpingtons. In owls the yellow eye is due to bright yellow granules in cells coating the iris

Brown and black eyes in birds are produced by a layer of branching cells on the iris containing dark pigment granules. Ruby eyes are produced in various ways in different birds; and some birds, such as certain birds of paradise, have particolored irides. Genetically, black due to pigmented iris is dominant over yellow and other grades of iris pigmentation.

Hollander and Owen (1939) show that in pigeons pearl is a simple recessive to the normal orange. Pearl, which is faintly yellow, accompanies the factor for chocolate plumage. Unlike fowls, the pigeon iris has no carotenoid pigment. Chemical tests also show no flavines or flavones. The yellow pigment is not xanthine but is probably melanin-like.

Hair Color

Reference has already been made to the hypothesis (p. 95) that the various types of eye and hair coloring as regards blond and brunet can be explained on the basis of one pair of factors (**E**) for eye color and another (**H**) for hair color, both of which act in the heterozygous or homozygous condition to produce time effects in color change. As we found it necessary to assume crossing-over between **E** and **H,** to account for the origin of the blond type, it is necessary to assume that these genes occupy different loci in the same pair of chromosomes. In that analysis red hair was included with the dark, but it clearly requires separate gene representation.

Various hypotheses regarding the relation of red to brown, black and blond hair have been formulated, so we must examine more closely the matter of hair pigmentation. Before taking up the genetics, it is necessary to consider briefly the structure of human hair. A hair is typically a tube; its bore is the medulla, which may contain pigment and minute air bubbles; its wall is the cortex, which may also contain pigment, and overlapping scales on the surface form the cuticle. It is well known that in wild animals such as the rabbit and guinea pig the hair is agouti, i.e., the hairs are banded with different colors. In man, the hairs of one head are generally regarded as uniform, but while this is not always true they are never banded, although sometimes multicolored. The medulla is variable; it may be continuous, more or less discontinuous or even absent. Wynkoop (1929) found that the type of the medulla is not correlated with the age of the person but with the diameter of the hair, those of widest diameter having the largest medulla while the smallest hairs have none. Brown (1942) has shown similar conditions in various types of mammalian hair. Hausman (1928) found that, from blond to black, the cortical pigment granules in each hair increase in number and tend to arrange themselves in ovate masses. In the blond-to-black series the pigment granules are melanin, the biochemistry of which is still inadequately known.

In a biochemical study of rabbits with various genotypical coat colors, Neumann (1937) concluded that the black, brown and yellow melanins are chemically so closely alike that they must have a common origin (cf.

Danneel, p. 257). Daniel (1938) made a spectrophotometric study of melanin from various genotypes in the albino series of mice and found that they differ only quantitatively. From black through brown to nearly colorless the absorption spectra were nearly identical. Dawes (1941), using similar methods, found that frog melanin is nearly or quite identical with mammalian melanin and the pigment from a horse melanoma. The red pigment of human hair is believed by Arnow (1938) to be an oxidation product of melanin. It appears that hair color is partly a matter of pigmentation and partly of light-interference. See also Jankowsky (1932), who studied the oxidation of pigmented hair with hydrogen peroxide and reviewed the whole subject. He concluded that rutilism (red hair or beard) can arise in racial crosses between blond and black hair.

Keers (1934), in an important study of hair color in Holland, found that in red hair the pigment was always diffuse, showing all nuances (under the microscope) from red to red-yellow and light red, whereas Saller (1927), who thought that red hair is recessive, states that in red-haired Malayans he found the red pigment both diffuse and in granules. In some colors of hair, brown pigment granules are also present. The shade of color results not only from the relative amounts of the two colors, but Keers showed that it also depends on the size, number and arrangement of the pigment granules, the amount of air in the hair, its diameter, the presence of a medulla, etc.

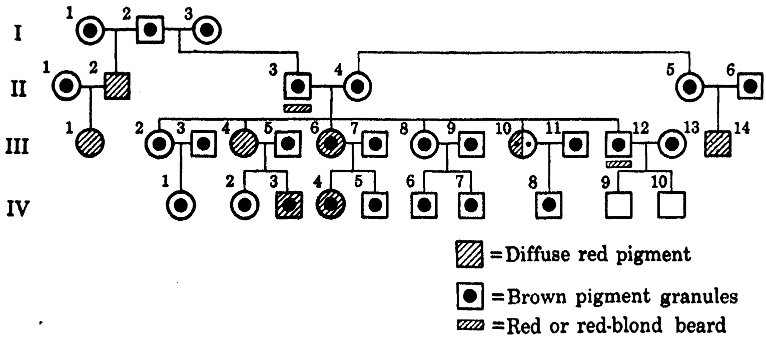


Fig. 30. Pedigree showing inheritance of red hair and beard. (After Keers)

Keers compiled two Jewish pedigrees of red hair, one of which is shown in Fig. 30. The red hairs showed no trace of granules. Case III. 10 had two kinds of hairs, i.e., with and without diffuse red pigment. Case III. 6 had both diffuse red pigment and brown granules in the hairs. Since II. 3, 4 had brown hair, red must be more or less hypostatic to brown, but both pigments can occur together, as in IV. 3, 4. Keers records the case of a boy (III. 12) with red hair which gradually changed to brown as he grew up. He retained some hairs with red and some without (diffuse) red pigment. His beard was red, and of course a reddish beard with brown hair is not uncommon. Two girls of nine and ten years had hair with diffuse red at the tips only. Keers' second family had red-blond hair with both diffuse red and dark-brown pigment granules. It is clear that pure red can be derived from (heterozygous) red-blond, a red-blond father and a blond mother having four children, one red-blond, two red and one dark blond. It appears that red and brown are both represented phenotypically in the hairs of an individual having both genes, so the case is something like that of Nabours' (1929) grasshopper color patterns. The epistatic effect of red on brown or blond could thus account for the many shades of red hair. There are probable differences also in the density or shade of the red pigment.

Saller (1927) found red hair not only in natives of Malaya but also in Melanesians of New Guinea. He also found small blond groups in Melanesia, and showed that Fischer's assumptions that red is dominant over non-red and that the red factor gradually changes brown to red, are wrong. Saller (1931b) finds red recessive to the brown series (blond to black) and assumes intensity factors to account for degrees of red. This is in accord with Rodenwaldt's Kisar hybrids, in which red is clearly hypostatic to black or dark hair. But Saller concludes that it is impossible at present to formulate a satisfactory theory of pigment inheritance in man. The Davenports (1909) found three families in which the parents and all the children had red hair. They concluded that red hair is recessive but with many exceptions. Saller suggested that the gene for red hair is allelic to the brown series. Scheidt (1925) records a German family (Fig. 31) in which eleven members in four generations had red hair and one red-blond, red being clearly dominant to blond hair. Ward (1938) found red hypostatic to brown in a family in three generations. The red hair was coarse and straight, the brown very fine in texture. Neel (1943) analyzed twenty-six families in which the parents had red hair and found it was due to an incompletely recessive factor hypostatic to black or dark brown. Probably not all genes for red hair are alike.

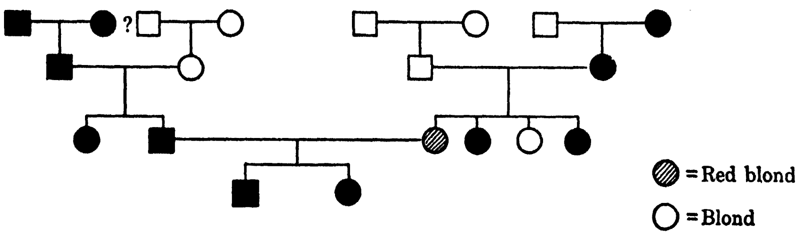


Fig. 31. Pedigree of red hair. (After Scheidt)

Bunak (1925) developed a colorimetric analysis of hair color, using the spectrophotometer for the measurement of spectral reflectance. I have not been able to see this paper. Gardner and MacAdam (1934) also used this method. The percentage of reflectance plotted against the wave length in mμ gives almost a straight line for black and blond hair, while for red hair it curves upwards in the green. By plotting the results, a line can be drawn between blond, red, and brown hair. Similar methods may serve in future for a much-needed scientific classification of hair colors. Up to the present, the difficulties have best been met by using a series of standard samples, as with eye colors. Trotter (1939) has given an account of the various classifications of hair color hitherto used.

In a study of the distribution of red hair according to age, Michelson (1934) found that in blond, brown and black hair red hairs may be present, sometimes only a few, sometimes in larger amounts. He examined hair clipped from the right temple of 2397 male whites and found a red component in 18 per cent. He also found some polychrome hairs, red at one end and black at the other. In twenty-seven persons there were black and red sections in the same individual hair, twenty-three persons had red and brown sections, eleven persons black and brown. This is probably a depigmentation phenomenon, the red tending to persist when the brown has disappeared. In general, an increase in redness was found from thirty-two to forty-seven years of age with minor fluctuations at later ages.

Bolk (1908a, b) made a survey of red hair in Holland. He examined nearly 500,000 children, omitting the Jews, and found about 2.5 per cent with red hair. Bolk concluded that rutilism is *sui generis* and not in the blond-black series. Table 9 shows the relations he found between eye color and hair color.

TABLE 9

EYE COLOR AND HAIR COLOR OF CHILDREN IN HOLLAND

		Hair Color (%)			
Eye Color	*Total*	*Blond*	*Brown*	*Black*	*Red*
Blue	186,033	83.34	11.81	2.38	2.47
Gray	152,072	79.67	14.66	3.06	2.63
Brown-green	58,531	60.68	28.64	8.00	2.55
Brown	82,338	45.05	38.61	14.28	2.03

Thus it appears that whereas blue or gray eyes tend to go with blond hair and brown eyes with brown or black hair, the proportion of red hair is constant for all eye colors. This indicates that the gene for red hair is located in a separate chromosome from the eye-color genes. Since the latter are linked with the blond-black hair-color series, it follows that red hair is an independent mutation which has become uniformly distributed at least in the Dutch population. Bolk

(1908a) divided hair colors into a *nigrochrome* series (flaxen to black) and a *chrysochrome* series (golden brown to fiery red). Brown is not fully epistatic to red. It is also recognized that the beard and moustache of men are often red when the head hair is black. This will be in men with the factors for both red and black. In the first extensive genetic study of hair color in man, the Davenports (1909) found two main types of hair pigment; (1) a reddish yellow varying to bright red (the pigment diffuse in the hair), (2) light yellow to brown and black. When both are present the brown may obscure the red. They found these colors in every degree of intensity and dilution, and they concluded that children never have darker hair than either parent. Also that red hair is a homozygous condition, the pigment being assumed to be a lipochrome. The dark red hair of the orang was found to be due to sepia-colored granules.

Philipchenko and Liepin (1913) made a considerable analysis of hair color in relation to eye color in Russia. They assume two factors, **B** and **C**, for black hair. Blond hair is then **bbcc** and chestnut hair is **BBcc, Bbcc, bbCC** or **bbCc.** Red hair is **bbcc** + a factor hypostatic to blond hair. They assume linkage of a factor for dark eyes and a factor (**B** or **C**) for dark hair. They found in the Leningrad population (Table 10)

TABLE 10

EYE COLOR AND HAIR COLOR OF CHILDREN IN LENINGRAD

Blue or gray eyes with blond hair	30.25%
Blue or gray eyes with chestnut hair	9.92
Brown or black eyes with black hair	42.84
Blue or gray eyes with red hair	2.21

In a study of eye and hair color and blood groups in the Netherlands, Bijlmer (1940) distinguished blue, gray or green, and brown eyes, with transitions between them. In green eyes a film of brown can be seen over the blue. Gray is also a mixed color with a very thin yellowish layer over the blue, but sometimes gray is due to gray bundles of connective tissue in the stroma of the iris. Among over three thousand persons examined, two had yellow eyes with dark blond hair. Bijlmer supports Bolk's conclusion that dark pigmentation of hair and eyes proceeds from the south and it may have reached the Netherlands partly from the sea, the eastern provinces being more blond. The Rhine and Meuse form a sharp boundary between brunet and blond types because the Roman influence, with brunet pigmentation, originally reached to this line.

Saller (1929) in a study of 114 gymnasts in Flensburg (Schleswig-Holstein) concluded that the type belonged to the Cromagnon race. The hair color was brown in 51.8 per cent, ash blond 30 per cent, red 1.8 per cent (compared with 69.4 per cent blond hair in Sweden and 15.6 per cent in Switzerland). Eye color was 86.3 per cent gray to blue and 12.7 per cent brown, light eyes generally being combined with light hair.

Keers (1934) postulates a series of alleles for red hair. He describes a family in which the mother was of Sumatran-Portuguese origin with very dark hair, and the father a Dutch blond. In four of their descendants both types of hair are present intermingled. In another family, with Italian mother and Dutch father, blond and dark hairs were interspersed in the heads of the children. This condition recalls that of roan cattle, a cross between red and white in which both types of hair are interspersed; or of certain plant hybrids in which the different types of epidermal hairs of the two parents are both present. In red-headed Malays, Saller (1927) found that the red and brown pigments were never present in the same hair. In Hauschild's scheme, the factors for red (**R**) and brown (**M**) give **RRMM** (chestnut brown), **rrMM** (brown), **RRmm** or **Rrmm** (red), **rrMm** (blond) and **rrmm** (colorless).

In a survey of the distribution of red hair, Conitzer (1931) finds 2 per cent or more in the population of Sweden, Denmark, Holland, the British Isles, Switzerland and Iceland; less than 1 per cent in the Mediterranean countries of southern Europe. The frequency in many parts of the world is unknown but he concludes that it is present in all races, although most frequent in Europe. In Gaboon, West Africa, Negroes have been recorded with black skin, clear red hair, eyebrows and eyelashes. Stefansson found red hair among the isolated Eskimos of Victoria Island, others have observed it in the Ainu, but it is very rare among Mongolians. Three red-haired Japanese were nevertheless recorded among 2361. Rutilism is also known in the Malay archipelago and New Guinea. Conitzer gives a number of pedigrees showing red-hair inheritance and postulates the following allelic factors: **R** for yellow-red pigment, $\mathbf{r}_1$ for yellow (weak red) pigment, **r** for lack of red pigment. He recognizes that the red may be obscured in the hair by black, but the red factor may then manifest itself in a red beard; also that two clear blond parents never have a red-haired child. The strong correlation between red hair and freckles of the skin is also recognized. Red hair is correlated with fair skin and light eyes but can occur with albinism, especially in the dark-skinned peoples. J. Bauer regarded freckles as a dominant character, but Skerlj (1930) mentions certain cases which contradict this conclusion.

It has generally been assumed that blond hair is lacking in melanin and that the graying of hair is a process of depigmentation or loss of melanin granules. Stary and Richter (1938) present quite a different view. On the basis of biochemical work they find that blond and white hair consists mainly of a *leucokeratin*, like that of the fingernails, of which even black hair has a little. Black hair contains mainly *melanokeratid*, a substance which consists of a protein portion separated from a melanin-like pigment by hydrolysis with acids. Blond, brown and black hair would then contain leucokeratin and melanokeratid in different proportions. This idea is very difficult to harmonize with the observed fact that melanin is contained in granules within the otherwise colorless hair. A third substance, *rhodokeratid*, is found in red hair.

Clay, Cook and Routh (1940) state that in eukeratins such as wool and hair the basic amino acids (histidine, lysine and arginine) are present in a relatively constant molecular ratio of 1 : 4 : 12, while the non-basic amino acids, especially cystine, show wide variations. They analyzed 120 samples of human hair and found that dark hair contained more cystine than light. More cystine and cysteine were found in the hair of males than of females. Red hair and that of an albino female showed no marked difference from hair of other colors, except that cystine was lower in albino hair than the average for light hair. Gray hair was not tested.

Sorby in 1878 showed that a red pigment could be extracted from bright red human hair, but not from animal hair, by mineral acids. Rothman and Flesch (1943) have recently found that the pigment of red human hair is a complex phenolic iron compound having OH attached to a heterocyclic ring containing N. It is a purplish red substance in acid pH, becoming brown in an alkaline medium. This confirms its independence of the brown melanin series.

E. Fischer (1939) bases his views of hair pigmentation on the work of Stary and Richter, and assumes that the whitening of hair is a hormonal process in which more leukokeratin than melanokeratin is produced. He suggests that when the genes for brown and red hair are both present the result is not a mixture but a brown-red keratin which is of different composition from either. He states that a mother with dark hair will often have a child born with dark hair, due to hormones circulating through the placenta. This falls out in a few weeks and is replaced by blond hair which may darken later. Until more is known regarding the chemical nature and relations of melanin and keratin it would be unsafe to erect an hypothesis of hair color on the basis of leukokeratin. It has to be remembered that melanin pigment occurs in the iris, the skin, and in diseased conditions may occur in many other parts of the body in the absence of keratin. Landois (1866) described a case of overnight graying of the hair and beard in a man with delirium tremens. He ascribed both sudden and slow graying to the formation of air bubbles in the hair shaft.

Some have assumed a colorless precursor of melanin. Gorter (1935) found that depigmentation of the fur of cats, rabbits and rats could be produced by absence of copper and that the pigment could be restored by the addition of copper to the diet. Copper may thus act as a catalyst to pigment formation. A Japanese has shown that in black human skin and hair the copper content is somewhat greater than in brown, which is again greater than in skin and hair of whites. Richter and Clisby (1941) found that phenylthiocarbamide, which is highly lethal to rats, produced definite graying and hyperthyroidism when given in small quantities. On returning to normal diet they slowly turned black again. Others have found that the vitamin B complex is concerned in hair depigmentation, and Sieve (1941) has found that small doses of *p*-aminobenzoic acid cause darkening of gray hair, while Oleson, Elvehjem and Hart (1939) found that liver extract was effective in preventing depigmentation of the hair. These results serve as sidelights on the biochemistry of hair pigmentation.

Wright (1941) has discussed the physiology of melanin formation in relation to mammal coat colors. There are indications that each gene intervenes at one or more definite points in a system of interacting chain reactions to affect the rate of the reaction. Melanin appears to be produced from tyrosin or allied substances, especially dopa (3-4-dioxyphenylalanine, a cyclo-amino-acid related to adrenalin), under the influence of oxidases. The dopa reaction is an indicator of the presence of the pigment-forming oxidase and hence the power to produce melanin. Bloch (1929) studied melanin formation in Addison's disease. He shows that in melanoblasts the pigment is formed only in the cytoplasm.

Kaliss (1942) has made a study of the process of pigmentation in the hair of the mouse. He finds that basically the physiology of pigment production is the same for all colors, i.e., oxidation of a melanogen such as tyrosine in the presence of an oxidase to form melanins. The pigment appears first as granular cytoplasmic inclusions in certain cells of the follicle. These granules range in size from the limits of resolution to 1.5 μ in diameter. The histogenesis of yellow and brown-black pigment is the same. In agouti hair the transition from one to the other is not sharp. There is no evidence of "colorless chromogens" in albinos nor in the white hair of piebald mice.

Bogart and Ibsen (1937) made a microscopic study of red, black and other hair colors in cattle (and guinea pigs) in relation to the factors **B, Bs, E, R** and **C,** the results of which will be useful for comparison with human hair color.

LITERATURE

Allan, J. 1905. Heterochromia iridis. *Brit. Med. J.* i. 990.

———. 1906. Heterochromia iridis. *Brit. Med. J.* i. 977–978.

Arnow, L. E. 1938. The acid-soluble pigment of red human hair. *Biochem. J.* 32:1281–1284.

Bamber, Ruth C. 1927. Genetics of domestic cats. *Bibliogr. Genet.* 3:1–86.

Bamber, Ruth C. 1933. Correlation between white coat color, blue eyes and deafness in cats. *J. Genet.* 27:407–413.

Beddoe, John. 1885. *The Races of Britain.* Bristol & London. Pp. 271.

Bijlmer, H. J. T. 1940. Contribution to the anthropology of the Netherlands. *Proc. Konink. Nederl. Akad. Wetens.* 43:113–139.

Bloch, Bruno. 1929. The problem of pigment formation. *Am. J. Med. Sci.* 177:609–618. Figs. 4.

Bogart, R. & Ibsen, H. L. 1937. The relation of hair and skin pigmentation to color inheritance in cattle, with some notes on guinea-pig hair pigmentation. *J. Genet.* 35:31–59. Pls. 4.

Bolk, L. 1908a. Heeft de roodharigheid de beteekenis van nuance of van varieteit? *Nederl. Tijdschr. Geneesk.* 52:216–230, 463–469, 643–646.

———. 1908b. Über die Verbreitung des Rothaarigen in den Niederlanden. *Zeits. f. Morph. u. Anthrop.* 11:139–152.

Bollag, L. 1927. Untersuchungen über die Vererbung von Mischfarben der Iris beim Menschen. *Arch. J. Klaus-Stift.* 2:191–205. Pl. 1.

Bond, C. J. 1912. On heterochromia iridis in man and animals from the genetic point of view. *J. Genet.* 2:99–129. Pls. 4.

———. 1919. On certain factors concerned in the production of eye colour in birds. *J. Genet.* 9:69–81.

Bosshart, H. 1939. Anthropologische Untersuchungen im Engstligen- und Frutigtal. *Arch. J. Klaus-Stift.* 14:1–194. Pls. 21, figs. 55.

Brown, F. M. 1942. The microscopy of mammalian hair for anthropologists. *Proc. Am. Phil. Soc.* 85:250–274.

Brues, A. M. 1939. Sibling resemblances as evidence for the genetic determination of traits of the eye, skin and hair. Ph.D. Thesis. Harvard.

Bryn, H. 1920. Researches into anthropological heredity. I. On the inheritance of eye colour in man. *Hereditas* 1:186–212.

———. 1926. Ueber die Augentypen in Norwegen und ihre Vererbungsverhältnisse. *Skr. utg. av Det Norske Vidensk-Akad.* No. 9, pp. 57, pls. 2.

Bullough, W. S. 1942. The reproductive cycles of the British and Continental races of the starling. *Phil. Trans. Roy. Soc. B.* 231:165–246. Pls. 10, figs. 52.

*Bunak, V. 1925. Ein Versuch der Bestimmung des Fenotypus der Haarfarbe mittels der Spectro-Photometrie. *Bull. Soc. Nat. Moscow, Sect. Biol. Exper.* 1:143.

Calhoun, F. P. 1919. Causes of heterochromia iridis with special reference to paralysis of the cervical sympathetic. *Am. J. Ophthal.* 2:255–269. Figs. 2.

Clay, R. C., Cook, K. & Routh, J. I. 1940. Studies in the composition of human hair. *J. Am. Chem. Soc.* 62:2709–10.

Conitzer, H. 1931. Die Rothaarigkeit. *Zeits. f. Morph. u. Anthrop.* 29:83–147.

Daniel, J. 1938. A spectrophotometric study of mouse melanin. *J. Genet.* 36:139–143.

Danneel, R. 1936. Die Färbung unserer Kaninchenrassen und ihre histogenetischen Grundlagen. *Zeits. f. Abst. u. Vererb.* 71:231–264. Figs. 18.

Davenport, C. B. 1927. Heredity of human eye color. *Bibliogr. Genet.* 3:443–463.

Davenport, G. C. and C. B. 1907. Heredity of eye color in man. *Science* 26:589–592.

Davy, John. 1861. Some observations on the albino. *Trans. Roy. Soc. Edinb.* 22:507–509.

Dawes, B. 1941. The melanin content of the skin of *Rana temporaria* under normal conditions and after prolonged light- and dark-adaptation. *J. Exper. Biol.* 18:26–49.

Ellis, R. W. B. 1931. Heterochromia of irides and hair. *Proc. Roy. Soc. Med.* 24:1057–1058.

Eskelund, V. 1938. Structural variations of the human iris and their heredity, with special reference to the frontal boundary layer. London: Lewis. Pp. 242.

Fantham, H. B. 1926. *S. Afr. J. Sci.* 23:635–636.

Fischer, E. 1939. Versuch einer Phänogenetik der normalen körperlichen Eigenschaften des Menschen. *Zeits. f. Abst. u. Vererb.* 76:47–117.

Fleischhacker, H. 1936. Über die Vererbung der Augenfarbe. *Zeits. f. Vererb. u. Konst-lehre* 19:643–666. Figs. 16.

Ford, E. B. and Huxley, J. S. 1927. Mendelian genes and rates of development in *Gammarus Chevreuxi. Brit. J. Exp. Biol.* 5:112–134, Pl. 1.

Freerksen, E. 1938. Die Struktur der menschlichen Iris und ihre Vererbung. *Zeits. f. Anat. u. Entw.* 109:207–229. Figs. 41.

Frets, G. P. 1925. Over de erfelijkheid van de oogkleur. *Genetica* 7:65–86.

———. 1932. Family investigations on the heredity of eye color in man. *Proc. 6th Internat. Congr. Genetics* 2:53–57.

———. 1935. Heredity of eye color in man. *Eugen. News* 20:1–3.

Galloway, A. R. 1912. Notes on the pigmentation of the human iris. *Biometrika* 8:267–279.

Galton, Francis. 1889. *Natural Inheritance.* London: Macmillan. Pp. 259.

Gardner, B. B. & MacAdam, D. L. 1934. Colorimetric analysis of hair color. *Am. J. Phys. Anthrop.* 19:187–201.

Gates, R. Ruggles. 1915. On the modification of characters by crossing. *Amer. Nat.* 49:562–569.

———. 1938. Blue eyes in natives of Ceylon. *Brit. Med. J.* i. 921–922.

Godin, P. 1933. Evolution de la "couleur des yeux" sous l'influence de la "puberté." *Bull. Acad. Med. Paris* 109:657–660.

Gorter, F. J. 1935. Depigmentation, a new dietary deficiency disease cured by copper. *Nature* 136:185.

———. 1935. Dietary depigmentation of young black and pied rats, promoted by rapid growth, prevented and cured by ingestion of copper. *Zeits. f. Vitamin-forsch.* 4:277–293. Figs. 8.

Gossage, A. M. 1908. The inheritance of certain human abnormalities. *Quart. J. Med.* 1:331–347.

Gray, John. 1907. Memoir on the pigmentation survey of Scotland. *J. Roy. Anthrop. Inst.* 37:375–401.

Gross, K. 1921. Ueber Vererbung von Augen und Haarfarbe und den Zusammenhang beider. *Arch. f. Rass. u. Ges.-Biol.* 13:164–175.

Hägler, K. 1941. Anthropologische Studie über die Bewohner des Tavetsch, eines alpinen Hochtals im Kanton Graubünden (Schweiz). *Arch. J. Klaus-Stift.* 16:1–224. Pls. 11.

Harland, S. C. 1936. The genetical conception of the species. *Biol. Revs.* 11:83–112.

Hausman, L. A. 1928. The pigment granules of human head hair. *Am. J. Phys. Anthrop.* 12:273–283.

———. 1934. Histological variability of human hair. *Am. J. Phys. Anthrop.* 18:415–429. Figs. 5.

Hesch, M. 1931. Ueber Pigmentierungsverhältnisse der menschlichen Iris nach Alter und Geschlecht. *Verh. Ges. Phys. Anthrop.* 5:9–25. Figs. 5.

Hollander, W. F. & Owen, R. D. 1939. Iris pigmentation in domestic pigeons. *Genetica* 21:408–419.

Hooton, E. A. 1940. Stature, head form, and pigmentation of adult male Irish. *Am. J. Phys. Anthrop.* 26:229–249.

Hughes, B. O. 1944. The inheritance of eye color in man — brown and nonbrown. *Contrib. Lab. Verteb. Biol.* No. 27. Pp. 10.

Hurst, C. C. 1908. On the inheritance of eye color in man. *Proc. Roy. Soc. B.* 80:85–96.

———. 1912. Mendelian heredity in man. *Eugen. Rev.* Pp. 25, figs. 6.

Iljin, N. A. 1926. Ruby eye in animals and its heredity (Russian). *Trudy Lab. Exp. Biol. Zooparka, Moscow* 1:107–129.

Jankowsky, W. 1932. Beitrag zur Frage der Haarpigmente. *Zeits. f. Rassenphysiol.* 5:1–48, 111–119.

Jochelson, W. 1928. Peoples of Asiatic Russia. *Mem. Amer. Mus. Nat. Hist.* Pp. 277, figs. 42, maps 10.

Kaliss, N. 1942. The morphogenesis of pigment in the hair follicle of the house mouse. *J. Morph.* 70:209–218. Pl. 1.

Karvé, I. 1931. Beobachtungen über die Augenfarben an Chitpavan-Brahmanen. *Zeits. f. Morph. u. Anthrop.* 29:498–501.

Keers, W. 1934. Über die Erblichkeit des menschlichen Kopfhaares. *Arch. f. Rass. u. Ges. Biol.* 27:362–389.

Kollmann, Dr. 1883. Die statistischen Erhebungen über die Farbe der Augen, der Haare und der Haut in den Schulen der Schweiz. *Nouveau Mem. Soc. Helvét. Sci. Nat.* 28. Pp. 42.

Kranz, H. W. 1926. Beobachtungen und Bemerkungen zum Heterochromie-problem. *Arch. f. Ophth.* 117:554–574.

Landois, L. 1866. Das plötzliche Ergrauen der Haupthaare. *Virchow's Arch.* 35:575–599. Pl. 1.

Lenz, F. 1921. Ueber geschlechtsgebundene Erbanlagen für Augenfarbe. *Arch. f. Rass. u. Ges.-Biol.* 13:298–300.

Lundborg, H. 1920. Sozialanthropologische Untersuchungen in Schweden. *Hereditas* 1:163–177.

Mann, Ida. 1931. The iris in the Vertebrates. *Trans. Zool. Soc. Lond.* 21:355–412. Col. pls. 5.

MacConaill, M. A. 1938a. The stature of male school children in relation to hair and eye colour. *Ann. of Eugen.* 8:117–125.

———. 1938b. Blood groups and pigmentation. *Nature* 141:923.

———. 1941. The classification of hair and eye colour upon developmental and genetic bases. *Ann. of Eugen.* 11:173–178.

MacConaill, M. A. & Ralphs, F. L. 1936. Post-natal development of hair and eye colour, with special reference to some ethnological problems. *Ann. of Eugen.* 7:218–225.

Martin, R. 1928. *Lehrbuch der Anthropologie.* Jena.

Maung, K. 1941. Discriminant analysis of Tocher's eye colour data for Scottish school children. *Ann. of Eugen.* 11:64–76.

Michelson, N. 1934. Distribution of red hair according to age. *Am. J. Phys. Anthrop.* 18:407–413.

Nabours, R. K. 1929. The genetics of the Tettigidae (grouse locusts). *Bibliogr. Genet.* 5:27–104. Col. pls. 2.

Nachtsheim, H. 1933. Die genetischen Beziehungen zwischen Körperfarbe und Augenfarbe beim Kaninchen. *Biol. Zentlbl.* 53:99–109.

Neel, J. V. 1943. Concerning the inheritance of red hair. *J. Hered.* 34:93–96.

Neumann, P. 1937. Haarpigmentuntersuchungen an verschiedenen Farbrassen des Kaninchens. *Biol. Zentlbl.* 57:522–550.

Nowak, H. 1932. Ein Stammbaum von erblicher Heterochromie der Iris. *Deut. Med. Wochens.* 58:94.

Oleson, J. J., Elvehjem, C. A. & Hart, E. B. 1939. Nutritional achromatrichia. *Proc. Soc. Exp. Biol. & Med.* 42:283–285.

Passow, A. 1932. Über gleichseitige Vererbung von sektoren-formiger Irispigmentierung, zugleich ein Beitrag zur Frage der gleichseitigen Vererbung überhaupt. *Arch. f. Rass. u. Ges.-Biol.* 26:417–421. Figs. 6.

———. 1934. Okulare Paresen im Symptomenbild des "Status Dysraphicus." *Münch. Med. Wochens.* 81:1243.

Pfitzner, W. 1897. Ein Beitrag zur Kenntnis der sekundärer Geschlechtsunterschiede beim Menschen. *Morph. Arb.* 7:473–514.

Philipchenko, J. & Liepin, T. 1913. Zur Frage der Vererbung von Augen- und Haarfarbe bei dem Menschen. *Bull. Bureau Eugenics, Petrograd* 1:10–14.

Przibram, H. 1908. Vererbungsversuche über asymmetrische Augenfärbung bei Angorakatzen. *Arch. f. Entw.-Mech.* 25:260–265.

Punnett, R. C. 1928. Further notes on Dutch and English rabbits. *J. Genetics* 20:247–260. Figs. 6.

Raper, H. S. 1926. The tyrosinase-tyrosine reaction. V. Production of *l*-3:4-dihydroxy phenylalanine from tyrosine. *Biochem. J.* 20:735–742.

———. 1927. VI. Production from tyrosine of 5:6-dihydroxy-indole and 5:6-dihydroxy-indole-2-carboxylic acid — the precursors of melanin. *Biochem. J.* 21:89–96.

Richter, C. P. & Clisby, K. H. 1941. Graying of hair produced by ingestion of phenylthiocarbamide. *Proc. Soc. Exp. Biol. & Med.* 48:684–687. Figs. 2.

Riddell, W. J. B. 1942. Studies in the classification of eye colour. *Ann. of Eugen.* 11:245–259.

Riddell, W. J. B. 1943. II. *Ann. of Eugen.* 12:24–30.

Roberts, E. 1945. Occurrence of red-eye in swine. *J. Hered.* 36:207–208. Figs. 2.

Rothman, S. & Flesch, P. 1943. Isolation of an iron pigment from human red hair. *Proc. Soc. Exp. Biol. & Med.* 53:134–135.

Saller, K. 1927. Erblicher Rutilismus in der Malayischen Inselwelt. *Zeits. f. Abst. u. Vererb.* 45:202–231.

———. 1929. Untersuchungen über Konstitutions- und Rassenformen an Turnern der deutschen Nordmark. *Zeits. f. Vererb. u. Konst-lehre* 14:151. Figs. 8.

———. 1931a. Eine neue Augenfarbentafel. *Zeits. f. Konst-lehre* 15:674–678. Col. pl.

———. 1931b. Über den Erbgang der Rothaarigkeit beim Menschen. *Zeits. f. Abst. u. Vererb.* 59:203–219.

Sawin, P. B. 1932a. Hereditary variation of the chinchilla rabbit. *J. of Hered.* 23:39–46.

———. 1932b. Albino allelomorphs of the rabbit with special reference to blue-eyed chinchilla and its variations. *Carnegie Inst. Publ.* No. 427.

Scheidt, W. 1925. Einige Ergebnisse biologischer Familienerhebungen. *Arch. f. Rass. Biol.* 17:129–148.

Schwägerle, F. 1938. Irisstruktur und Augenfarbe bei ein- und zweieiigen Zwillingen. *Zeits. f. Vererb. u. Konst.* 22:545–577. Figs. 24.

Sedgwick, W. 1861. On sexual limitation in hereditary disease. *Brit. & Foreign Med.-Chirurg. Rev.* 27:477–489, 28:198–214.

Sichel, Dr. 1847. Note sur un rapport remarkable entre le pigment des poils et de l'iris et la faculté de l'ouie chez certains animaux. *Ann. des Sci. Nat. Zool.* Ser. 3, 8:239–241.

Sieve, B. F. 1941. Clinical achromatrichia. *Science* 94:257–258.

Skerlj, B. 1930. Beiträge zur Anthropologie der Slowenen. *Zeits. f. Morph. u. Anthrop.* 28:213–237.

Souter, W. C. 1906. Heterochromia iridis. *Brit. Med. J.* i. 1219.

Staffe, A. 1922. Untersuchungen über asymmetrische Augen und Haarfarbe der Schulkinder des Kuhländchens. *Arch. f. Rass. u. Ges.-Biol.* 14:305–314.

Staples-Browne, R. 1908. On the inheritance of colour in domestic pigeons with special reference to reversion. *Proc. Zool. Soc. Lond.* 1908: 67–104.

Stary, Z. & Richter, R. 1938. Das Leukokeratin und die Chromoproteide des Menschenhaares. *Hoppe-Seyler's Zeits. f. physiol. Chem.* 253:159–169.

Steggerda, M. 1930. The inheritance of eye-color. *Eugen. News* 15:175.

Streiff, J. 1919. Beobachtungen und Gedanken zum Heterochromieproblem. *Klin. Monatsbl. f. Augenhlk.* 62:353–390.

———. 1932a. Revision älterer und neuer Befunde zum Verständniss der echten Früh-Heterochromie. *Klin. Monatsbl. f. Augenhlk.* 88:751–761.

———. 1932b. Zur Uebereinstimmung und Nichtübereinstimmung der Haut-, Haar- und Augenfarbe, und über den Erbanteil der Uvea und den Anteil des Sympathikus an der schliesslichen Gestaltung und Färbung der Iris. *Klin. Monatsbl. f. Augenhlk.* 88:577–600.

Tjebbes, K. 1924. Crosses with Siamese cats. *J. Genet.* 14:355–366.

Tocher, J. F. 1908. Pigmentation survey of school children in Scotland. *Biometrika* 6:129–235. Pls. 26.

Trotter, Mildred. 1939. Classifications of hair color. *Am. J. Phys. Anthrop.* 25:237–260.

Usher, C. H. 1920. Histological examination of an adult human albino's eyeball, with a note on mesoblastic pigmentation in foetal eyes. *Biometrika* 13:46–56. Pls. 2.

Vogt, A. 1938. Weitere Augenstudien an eineiigen Zwillingen höheren Alters über die Vererbung der Altersmerkmale. *Klin. Monatsbl. f. Augenhlk.* 100:497–544. Figs. 123.

Wagensail, F. 1931. Anthropologische Untersuchungen an anatolischen Türken. *Zeits. f. Morph. u. Anthrop.* 29:193–260. Pls. 8.

Ward, T. 1938. Variation in hair color and texture. *Eugen. News* 23:10.

Wellington, R. H. 1906. Heterochromia iridis. *Brit. Med. J.* i. 1219.

Weninger, J. 1934. Irisstruktur und Vererbung. *Zeits. f. Morph. u. Anthrop.* 34:469–492.

Wessely, K. 1932. Über geflechte (getigerte) Iris. *Klin. Monatsbl. f. Augenhlk.* 88:245.

Winge, O. 1921. On a partial sex-linked inheritance of eye color in man. *Compt. Rend. Lab. Carlsberg* 14, No. 12, pp. 23.

Wright, Sewall. 1918. Color inheritance in mammals. IX. The dog. *J. Hered.* 9:87–90.

———. 1941. The physiology of the gene. *Physiol. Revs.* 21:487–527.

Wynkoop, E. M. 1929. A study of the age correlations of the cuticular scales, medullas, and shaft diameters of human head hair. *Am. J. Phys. Anthrop.* 13:177–187.

Chapter VI

THE INHERITANCE OF COLOR-BLINDNESS

PERSONS with normal vision can distinguish about 165 shades of color in the spectrum, while to the color blind particular zones appear more or less weak or colorless. Vision may be defective for any of the four primary colors, red, green, yellow and blue, or for all of them. Red-green and yellow-blue form complementary pairs in different types of color-blindness. The normal eye is totally color blind at the periphery of the field of vision, the adjacent zone being red-green blind. In color-blind persons the condition is more marked when they are fatigued.

From the point of view of color vision, persons are sometimes classified as monochromats, who are totally color blind, dichromats and (normal) trichromats. The dichromats or color blind are again classed as protanopes and deuteranopes (both of which fail to distinguish colors in the red-green region of the spectrum and differ in their luminosity curves) and tritanopes, who cannot distinguish colors in the blue-green. These various types will be considered later.

The ordinary types of color-blindness are now well known to be inherited as sex-linked recessives, the gene being in the X-chromosome. This is transmitted by a father to all his daughters, who are therefore heterozygous for the condition. The daughters are nevertheless generally normal in color vision since the condition is recessive. A son always receives his X-chromosome from his mother. Since the mother has two X-chromosomes, one of which carries the gene for color-blindness, half the sons of the daughters of a color-blind man will, on the average, be color blind. Until the role of the X-chromosome in determining sex was understood this method of inheritance seemed quite mysterious, but it is now clear that the gene merely follows the path of the X-chromosome from one generation to the next. Wilson (1911), in a classical paper, first expressed the sex-linkage hypothesis when the history of the X- and Y-chromosomes had become clear both in meiosis and fertilization (see diagram, Fig. 4, p. 11).

Red-green color-blindness was formerly known as *Daltonism*, because Dalton the chemist was color blind and in 1794 described his own color sense anomaly.[1] The earliest record of this kind appears to be that communicated to the Royal Society in 1778 by the Rev. Michael Lort. It consists of a letter from Mr. J. Scott to the Rev. Mr. Whisson, of Trinity College, Cambridge, describing his infirmity and stating which of his relatives possessed it. This was thrown into the form of a pedigree chart by Cole (1919) and is shown in Fig. 32 with the addition of the X- and Y-chromosome symbols, X indicating one which carries the gene for color-blindness. No. III. 3 is the deponent and it will be seen that his father and his mother's brother were also color blind. His mother had a color-blind son and daughter and she must therefore have been heterozygous for the condition. The daughter III. 2 was homozygous for color-blindness and must therefore transmit the condition to *all* her sons, while all her daughters will be carriers. IV. 1 and 2 had in fact a normal sister who is not represented in the pedigree.

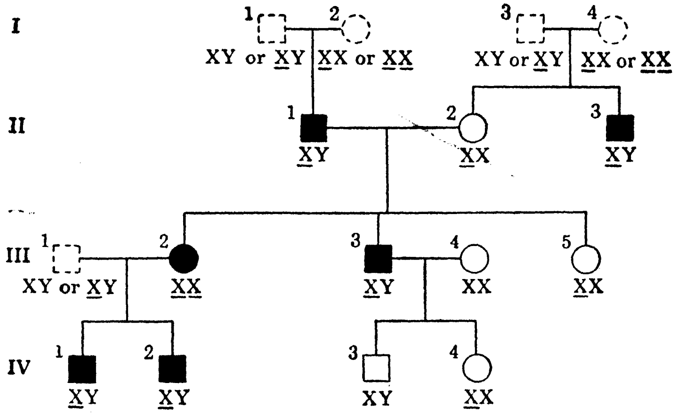


Fig. 32. An early pedigree of color-blindness.

Fathers, on the other hand, never transmit the defect to their sons. They are sons because they have received a Y and not an X from their father, and the gene for color-blindness is not contained in the Y. Regarding the deponent's grandparents there is no record, but probably both the grandmothers were heterozygous transmitters. This is by far the most likely interpretation and it resulted in III. 2 being homozygous for color-blindness — a rare condition in women.

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[1] I am indebted to Dr. E. G. Conklin for pointing out that a copy of this classical paper is in the Library of the Marine Biological Laboratory at Woods Hole. Dalton and one brother were affected, another brother and a sister normal. He found a laurel leaf "a good match to a stick of red sealing-wax"; also "no material difference between pink and light blue by day, but a striking contrast by candle-light."

In the famous paper of Clerk Maxwell (1855) on color vision and color-blindness he considered the theories of Newton, Young and Helmholtz on color vision and tested color-blind persons with the pure spectrum. He says, "it appears that though the red appears much more obscure than other colors, it is not wholly invisible, and, what is more curious, resembles the green more than any other color. The spectrum to them (the color blind) appears faintly luminous in the red; bright yellow from orange to yellow, bright but not colored from yellow-green to blue, and then strongly colored in the extreme blue and violet, after which it seems to approach the neutral obscure tint of the red. It is not easy to see why an insensibility to red *rays* should deprive the green rays, which have no *optical* connection with them, of their distinctive appearance. The phenomena seem rather to lead to the conclusion that it is the red *sensation* which is wanting, that is, that supposed system of nerves which is affected in various degrees by all light, but chiefly by red." He proceeds to test this hypothesis on four color-blind men with satisfactory results. Maxwell contrived an interesting pair of spectacles for the color blind, one glass being red, the other green. By using them, the difference between red and green could be clearly perceived. It is not necessary to enter into modern theories of color vision here, but it may be stated that there are still adherents of both the Young-Helmholtz and the Ladd-Franklin theories. The former theory requires three sets of sensory receptors in the retina or of optic nerve fibres, related to the sensations of red, green and violet. Le Gros Clark (1940) finds evidence that the six layers of cells in the lateral geniculate body in man and higher primates are related to color vision. In a recent discussion, Holmes (1945) concludes that there is an exact geometric or point-to-point projection of the retina on the cortex of the striate area, but that its functional organization is to some extent plastic and modifiable. For recent work on the physical chemistry of color vision see Sheppard (1945).

The rods of the retina function in a dim light, the cones in a bright light and in color vision, the rods being mainly sensitive at lower wave lengths. Hence in passage from a dim to a bright light the sensitivity of the eye shifts towards the red. The fovea, a small central area of the retina, has only cones, while the macula lutea, around the fovea, contains yellow pigment. Vision in a bright light uses chiefly the macular cones, in a dim light the macular and paramacular rods, the sensitivity of the rods and cones being related to the photosensitive pigments, rhodopsin and iodopsin. The lens in man is yellow (Wald, 1945), the cornea and ocular humors of the eye also absorbing some of the violet and ultra-violet rays. When the lens is removed for cataract, the aphakic (lensless) eye gains enormously in sensitivity to the violet and ultra-violet. In 1938 it was discovered that aphakic persons see very well in the ultra-violet, seeing it as blue or violet. The pigmentation of the lens varies greatly in persons of the same age.

Sedgwick in 1861 wrote a paper on "sexual limitation in hereditary disease," which recognized the essentials of what we now call sex-linked inheritance. He states that inability to distinguish colors is often associated with inability to distinguish sounds, and cites a family in which all the color-blind members were also stone deaf.

Horner, a Swiss ophthalmologist, in 1876 determined the law of color-blind inheritance, which is sometimes known as *Horner's Law.* In two pedigrees he showed that Nasse's Law for hemophilia applied to color-blindness. There was great interest in the subject at that time, a railway disaster in Sweden in 1875 having been caused by the color-blindness of the locomotive driver. His pedigree of "Daltonism," with fifteen cases in eight generations, is shown in Fig. 33. The *Centralbl. f. prakt. Augenhlk.* for 1878 contains numerous papers on color-blindness in Germany, Norway and other countries.

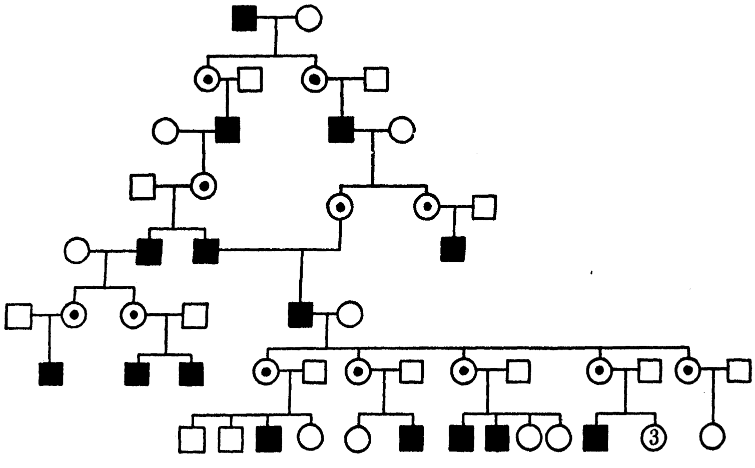

Fig. 33. Horner's pedigree of Daltonism.

Pole (1893), in a memoir on color-blindness, summarized the literature up to that time. He shows that achromatic vision or total color-blindness was already recognized as a very rare condition, that red-green was found to be the usual form of color-blindness, being known as *dichromatic vision,* but that aberrant forms of defective color vision were already known. The literature of the subject is separately treated (Pole, 1895) and in this connection is given an account of a family with many cases of Daltonism which has not found its way into the modern literature. Unfortunately the numbers of children are not given in all cases. The families were large (up to sixteen children) and twelve cases of color-blind men (with eleven normal brothers) are cited in four generations, the family (a very intelligent one) being traced through six generations. In every case the law of color-blind inheritance as now known was strictly followed. In fact the family recognized the law that sons of a color-blind man and their descendants are free, whereas the daughters though unaffected will transmit to some of their sons. The information was all collected from the family records by one member of the family in the fifth generation. Pole also cites a rare case of von Hippel, who described a young man whose left eye was normal while his right showed dichromatic vision.

An extensive pedigree of color-blindness, the particular type of which was not determined, was given by Bowditch (1922). It consists of three allied families with twenty cases (two of them female) in five generations (Fig. 34). I. 1 had "defective eyesight" and was probably color blind. IV. 1 was a professor of physiology and an authority on the physiology of vision. In family two the two sisters II. 5, 6 were color blind, but the condition of their parents is unknown. The father must have been color blind and the mother a carrier. The two color-blind sons, III. 6, 8 married sisters of III. 1. V. 12 married a son of IV. 1 in family one. The inheritance is strictly sex-linked recessive throughout. Nettleship (1906) described six cases of color-blind women. The pedigrees of four showed that they had color-blind fathers and color-blind sons.

The terms used for the different forms of color-blindness can most conveniently be defined as follows: *Deuteranopia* is green blindness, *Deuteranomaly* is green weakness, *Protanopia* is red blindness, *Protanomaly* is red weakness. In addition there are genes for extreme deuteranomaly and extreme protanomaly. In red-green blindness or dichromatic vision a neutral band appears in the green or blue-green. On either side of this band the spectrum appears of one color, varying only in brightness. To the red-blind or protanopes the spectrum appears shortened at the red end, which seems very dark or black. To the green-blind or deuteranope this end of the spectrum is about as bright as to the normal eye. Martin and Wright (1935) studied the quantitative aspects of color-blindness. They concluded that the discrimination of the deuteranope and the normal trichromat is approximately the same in the blue-green. The discrimination of the protanope is not so good nor is his range of color so large as that of the deuteranope. They found that the latter could distinguish only fifteen colors, protanopes twelve and normal persons forty-three.

Vogt (1922) gives one of the first pedigrees in which the different

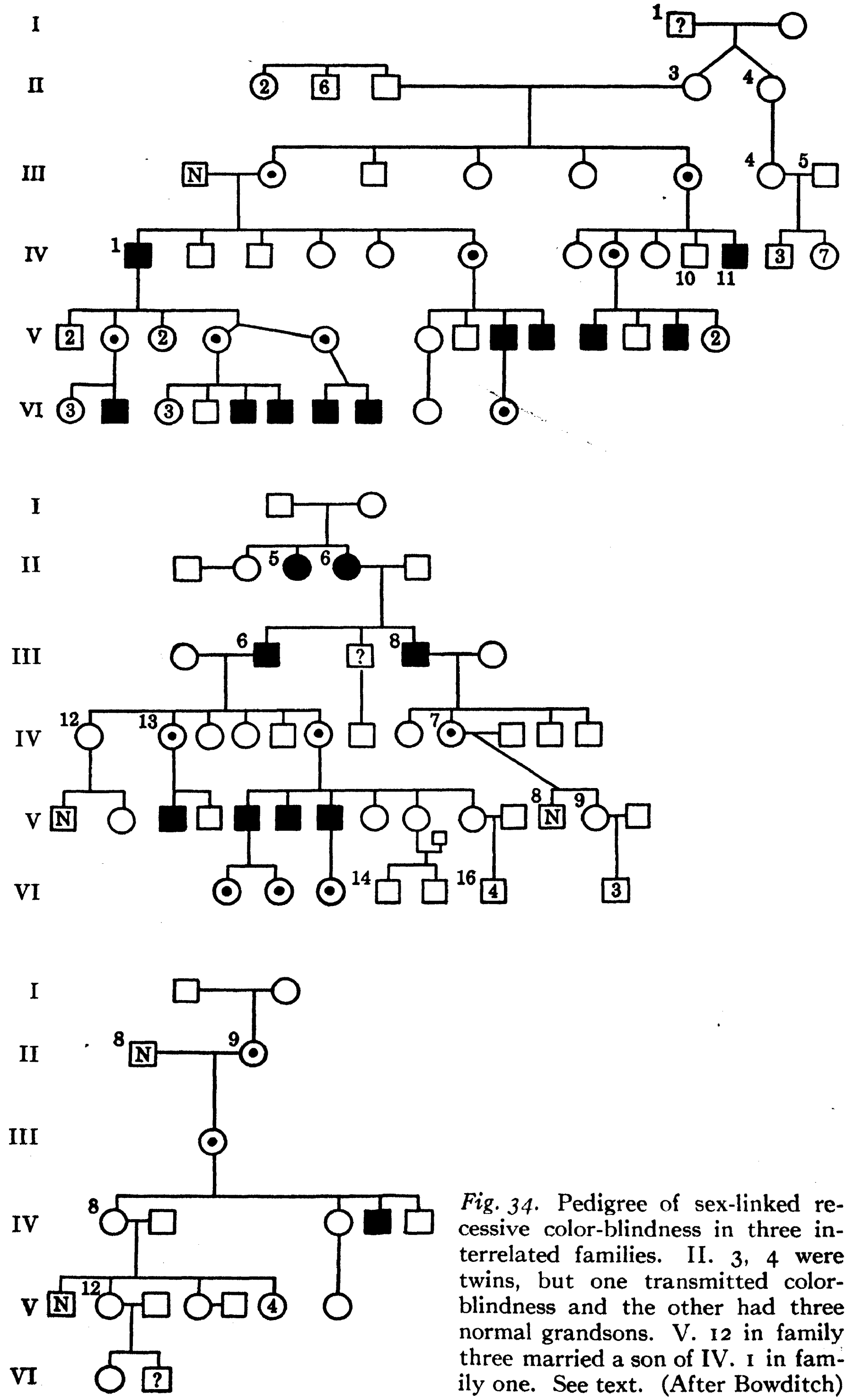

Fig. 34. Pedigree of sex-linked recessive color-blindness in three interrelated families. II. 3, 4 were twins, but one transmitted color-blindness and the other had three normal grandsons. V. 12 in family three married a son of IV. 1 in family one. See text. (After Bowditch)

forms of color-blindness are clearly recognized (Fig. 35). In this family, I. 5 and IV. 2 both had protanopia, III. 4 deuteranopia. From this it follows that protanopia is dominant to deuteranopia. In the Hu family of Vogt and Klainguti (1922), again two families carrying dichromacy have intermarried (Fig. 36). I. 2 and I. 4 were evidently conductors and I. 3 must have been color blind although there is no record of his condition. II. 7 × II. 8 represents the cross $\underline{X}Y \times \underline{X}\underline{X}$. Hence all the children will be color blind. In the third generation, the children marked with a ? were too young to be tested. In addition to the above marriage between two dichromatics, in five other families female dichromacy came from a carrier marrying a color-blind man, but it was not fully determined how protanopia and deuteranopia behave when crossed together. Just (1925) suggested that the four types of defective color vision were all alleles, with dominance relationships represented by $A_1 > A_2 > A_3 > A_4$.

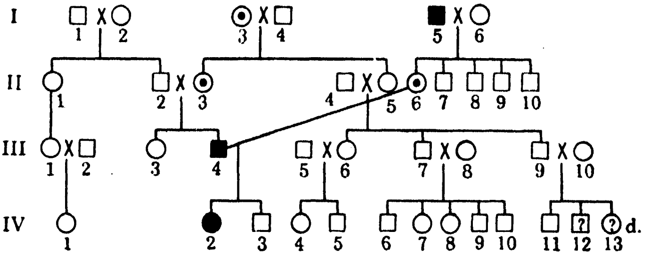

Fig. 35. Pedigree of red-green color-blindness. (After Vogt)

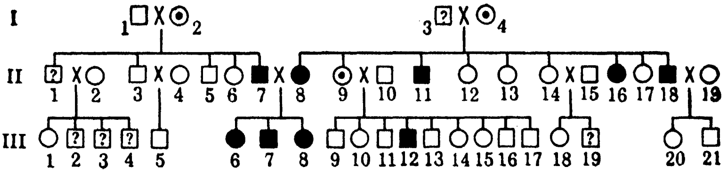

Fig. 36. Pedigree of color-blindness. (After Vogt and Klainguti)

Normal color vision is sometimes spoken of as *trichromacy*, and before the types of color defect were classified particular cases were sometimes regarded as anomalous trichromacy. This applies to an ordinary pedigree of weak vision for green (deuteranomalia) published by Wölfflin (1923). The four brothers in generation II were very similar in degree of green weakness. In another pedigree (Fig. 37) the two brothers in generation II show deuteranomaly, while III. 3 is a deuteranope, i.e., the condition is stronger than that transmitted by his mother. This appears to be a mutation from deuteranomaly to deuteranopia. On the other hand, III. 8, who shows deuteranomaly, must have inherited it from her mother, whose father was a deuteranope. In this case the change in intensity has been in the opposite direction. Döderlein (1922) had a different case. The father showed weak green vision, the mother transmitted green blindness. They had one normal son, two green-blind sons, one normal daughter and one with weak green vision. This daughter would be heterozygous for both types of green-vision defect and since deuteranomaly is dominant to deuteranopia she would be expected to show weak green vision.

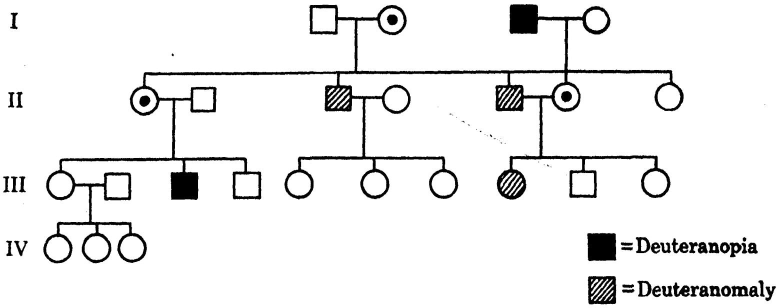

Fig. 37. Pedigree of color-blindness showing mutation from deuteranomaly to deuteranopia and *vice versa.* (After Wölfflin)

Waaler (1927a) made important contributions to the genetic relationships of the four color-vision defects. He cites a case of marriage between a man with protanomalia and a conductor (woman) for protanopia. They had a daughter with protanomalia, showing that this condition is dominant to protanopia. Among fifty-nine color-blind brother groups, fifty-five had the same type of color deficiency. In each of these cases the mother transmitted to her sons one definite color defect. In two brother groups both deuteranopia and deuteranomaly were present. These mothers would both be carrying one X with the gene for deuteranopia, the other X containing the gene for deuteranomaly. They were both color blind, showing deuteranomaly, which is dominant to deuteranopia. Two other groups of brothers contained a case of deuteranomaly and a protanope. The mothers in this case also would carry two affected X-chromosomes, but they were not color blind. From this it follows that while protanopia and protanomalia form one pair of alleles and deuteranopia and deuteranomalia another pair, these pairs are probably at different loci in the X-chromosome. The relative frequency of the different types of color defect are given by Waaler.

Julia Bell (1926) made an exhaustive collection of the material of color-blindness up to the date of her paper.

Waaler (1927b) tested the eyes of 18,121 school children in Oslo and studied the relatives of those who were color blind. Usually only one kind of color vision defect is found in a family, but all four types occurred in different families. When a homozygous woman occurred in a family she was phenotypically the same as the (hemizygous) men in her pedigree. It was found that normal is not fully dominant over deuteranomaly and that protanomaly and deuteranomaly are probably not fully dominant over protanopia and deuteranopia respectively. Waaler concluded that women who are heterozygous for color vision, i.e., protanope-deuteranope, protanope-deuteranomalous, protanomalous-deuteranomalous, or protanomalous-deuteranope would be clinically normal. Franceschetti (1928) made use of Waaler's results to draw conclusions regarding the dominance relations as follows:

Normal > protanomaly > extreme protanomaly > protanopia.
Normal > deuteranomaly > extreme deuteranomaly > deuteranopia.

He applied Goldschmidt's theory of multiple alleles with quantitative differences, but protanopia and protanomalia are apparently not alleles to deuteranopia and deuteranomalia, nor do they show transitions.

Brunner (1930), in a very lucid paper, found among 150 mothers of color-blind sons 9 who were not normal in color sense. His results are in accord with Waaler's hypothesis, but he points out that direct proof of its correctness would only be attained if union between a family with deuteranopia and one with protanopia produced a daughter with normal color vision. Other cases lead to the conclusion that extreme deuteranomaly and extreme protanomaly are determined by special genes. The members of the red-series and the green-series are regarded as quantitatively different, but intermediates between these inherited conditions do not occur. The two series (represented by protanopia and deuteranopia) are qualitatively different from each other. No mutation from normal to color blind was ever observed. Brunner's large pedigree

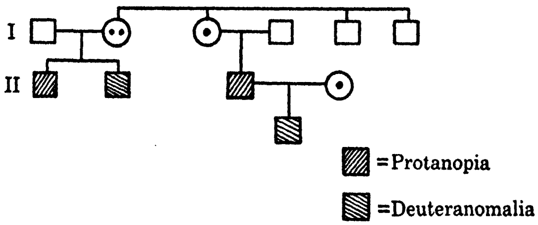

Fig. 38. Inheritance of protanopia and deuteranomalia. (After Brunner)

contains many cases of two forms of color-blindness united in the same woman. In one family both protanopia and deuteranomalia were present (Fig. 38). The brothers, II. 1, 2, were of these two types and their mother must have been heterozygous for both; the clinical condition of her eyes is unknown. Her sister transmitted protanopia to her son, whose wife must have been heterozygous for deuteranomalia.

Some of these relationships are visualized in Fig. 39, which indicates the positions of the genes in the X-chromosomes and their dominance relations.

N > P > D
N > DA > EDA > D
N > PA > EPA > P

P = protanopia
D = deuteranopia
PA = protanomalia
DA = deuteranomalia
EPA = extreme protanomalia
EDA = extreme deuteranomalia

A woman was found by Brunner who was **DA–PA.** She had a **DA** and a **PA** son, and her sight was normal in accordance with Waaler's hypothesis. Two women were **DA–EDA.** One of them was clinically **DA** in accord with the theory that the weaker departure from normal is dominant over the stronger. The other woman, however, was phenotypically **EDA.** Brunner explains this case as either a quantitative mutation from **DA** of the mother to **EDA** in the son, or as a variation in dominance. Another woman whose sons were **EDA** and **D** was clinically **D.** The dominance relations of the extreme forms to the other forms of color-blindness therefore remain more or less uncertain.

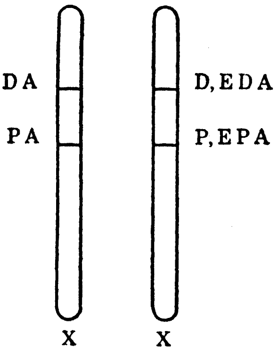

Fig. 39. Relative positions of genes for different forms of color-blindness.

Baetjer (1929) cites a case of a girl who was fully color blind,[2] as shown by tests with Ishihara, Stilling and Eldridge-Green color charts and the Holmgren Worsted test. She had a color-blind brother. Schmidt (1934) examined 35 women with color-blind sons. They were heterozygous for the following conditions: 5 were **DA,** 12 **EDA,** 5 **D,** 1 **PA,** 6 **EPA,** 6 **P.** None showed any departure from normal with the Ishihara color charts and the anomaloscope, but the conductors for **DA** more often showed uncertainty in reading the charts. The **D**- and **P**-groups of carriers however, showed a difference in their spectral curves of brightness. **D**-carriers were indistinguishable from normal (maximum at 590 $\mu\mu$), while in the **P**-group carriers the maximum was at 570 $\mu\mu$. Meyer (1932) finds that **P** and **PA** males are less sensitive to blue and yellow than **D** and normals.

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[2] Not totally color blind, which means absence of all color vision.

Brunner has a number of pedigrees showing the inheritance of particular forms of color-blindness. In all the work only four cases were found of a **DA** daughter with a normal father. These are explained by the principle *Pater semper incertus*, but they might be cases of irregular dominance or mutation.[3] On the assumption that the red series and the green series of alleles are at different loci of the X-chromosome, crossing-over between them might be expected to occur in the female, which might produce occasional sons with peculiar color vision, or with normal vision from a mother who was doubly heterozygous.

From a study of published pedigrees, Little and Gibbons (1921) found a marked excess of color blind in sibships, the number being 106 observed to 90 expected. In hemophilia they found an even greater excess, 551:457. They suggest that in these families a sex-linked lethal factor eliminates the normal males, leaving an excess of abnormals (see also Chap. XIV).

Davenport (1930), in an extensive survey of sex-linked inheritance in man, made a useful summary of some of the earlier literature of color-blindness. Trendelenburg and Schmidt (1935) examined 129 cases of color-blindness: 26 per cent were protanopes, 13 per cent deuteranopes, 13.3 per cent protanomaly, 47.7 per cent deuteranomaly. From these and Waaler's results it seems clear that deuteranomaly is the most frequent of the four conditions. A pair of identical twins were protanomalous and agreed as closely as the two eyes of an affected person.

Blue-yellow color-blindness or *tritanopia* is an extremely rare condition whose genetic relation to the other forms is at present unknown. There are few cases on record. Red and green can be distinguished, but in tests yellow and blue are matched with each other and with gray. The condition is sex-linked in inheritance, but its relation to the red-green series of alleles is unknown. Stilling (1878) described a case in which there was color-blindness not only for blue and yellow but also for violet and a large part of the green. A girl distinguished red from green but not blue from black, blue from gray or red from brown. Engelking (1926) described three cases (men) in a family in two generations, the condition being recessive sex-linked.

Nelson (1938) has made a critical analysis of the color vision of six deuteranomalous observers and one man with protanomalia, using the pure spectrum. The six did not agree among themselves, from which it is concluded that anomalous forms of trichromatism are intermediate between dichromatism and normal color vision. While this shows more variation than had previously been found, there is no reason to doubt that each type of color-vision defect is transmitted as a unit. Whether these smaller differences within the deuteranomalous group are inherited remains to be seen. One showed nearly full tritanopia or yellow-blue defect, but slightly bluish and slightly yellowish red were also indistinguishable. Oloff (1935) described a case of anomalous blue trichromacy in a woman.

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[3] Rath (1938) records an apparent mutation from normal to deuteranopia in a woman wh transmitted it but whose ancestors were not color blind.

We have already seen that in general one gene produces a color-blind condition in the male while two are necessary in the female, because the various forms of color-blindness are recessive to normal. Occasionally, however, women who are heterozygous for a color-blind gene nevertheless exhibit the condition. The dominance of the normal gene is frequently not absolute. Siemens (1926) cites a case of a color-blind mother (deuteranomaly) who had a normal daughter and a normal son. If she was homozygous for a color defect, all her sons would be color blind. Probably she was heterozygous, but color blind because of variable dominance. On the contrary, Wölfflin (1923) examined twelve carriers and found no kind of departure from normal. Wieland (1933), using very careful methods, found that some women heterozygous for all the various types of color vision defects showed a higher specific color threshold. In the deuteranope group about 14 per cent showed a higher threshold for red and 6 to 28 per cent for green. Among protanope carriers there is a higher threshold for red in *ca.* 40 per cent and for green in *ca.* 12 per cent. This supports the predictions of Nettleship and of Fleischer that carriers would show aberrant color vision. Pickford (1944) finds evidence that women who are heterozygous have a measurable red-green weakness.

Schinz (1941) suggests that the polyalleles for color defect are in a labile condition. He cites a pedigree of Brunner in which **DA** must have mutated to **D.** The mother transmitted **DA** to two sons and two daughters. The eldest son was **D,** so that a mutation from **DA** to **D** must have taken place. He points out that in two other Brunner pedigrees a mutation must have occurred, **DA** → **EDA** and **P** → **PA** or **PA** → **P,** which substantiates his view of the lability of these genes. The following mutations can occur: **PA** ⇌ **EPA** ⇌ **P, DA** ⇌ **EDA** ⇌ **D.** But there are no mutations between the **P** and the **D** series.

A remarkable case of female-sex-linked inheritance was described by Cunier (1839), in which color-blindness is inherited from mother to daughter only through five generations (Fig. 13, p. 28) in a Belgian family. Schiötz (1920) thinks the case is uncertain as it was before the ophthalmoscope came into use, and other defects were also present. Several investigators (Levit and Serebrovsky, 1929; Haldane, 1932; Gowen, 1933) have pointed out that the condition would be explained if the two X-chromosomes of the females were united at one end, as is known to be the case in certain strains of Drosophila (L. V. Morgan, 1922). Certain women would then be $\widehat{XX}Y$, the attached X's passing into the same gamete. The genes in the Y-chromosome might also have some effect on the individual. Such a woman might be expected to produce the four types of offspring in Fig. 40, i.e., daughters like herself and normal sons together with XXX superfemales and YY supermales. The latter might perhaps be non-viable, from analogy with known conditions in animals, and the former might also possibly be non-viable. This is by no means certain, however, because an X added to the forty-eight chromosomes already present in man would cause far less disturbance than one added to the eight chromosomes that make up the genome of Drosophila. If, on the other hand, a color-blind man married a woman with attached X's the children would be as indicated in Fig. 41. That is, all his sons and none of his daughters would be affected, but some of the latter might be transmitters. It is a not unreasonable assumption that XXY females exist.

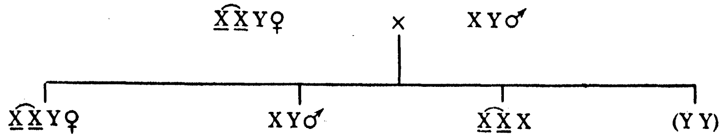

Fig. 40. Results of a cross between a color-blind woman with attached X-chromosomes and a normal man.

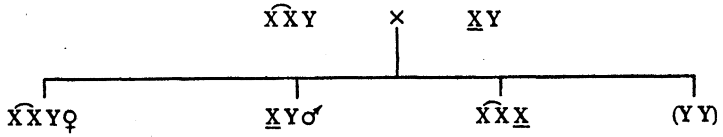

Fig. 41. Results of a cross between a normal woman with attached X's and a color-blind man.

Their existence could be shown if other pedigrees similar to this of Cunier are found in the future. Haldane (1932) cites certain pedigrees of sex-linked ichthyosis, hemophilia, amaurosis and senile cataract which may be interpreted as cases of a family with joined X's in the female, but there is great need of more evidence. By crossing-over between the attached X's it would be possible to derive a homozygous color-blind female with attached X's from an ordinary heterozygous color-blind woman. Just (1934) claims that a color-blind woman who had a normal son must have been homozygous for color-blindness and had attached X's which both went into the polar body, leaving the egg cell with no X. The son, if he got an X from his father, would be XO and possibly sterile; he could have no XY sons. If he got Y from his father he would be YO (possibly lethal), and his daughters would be XO. This woman's father was color blind, but there is no evidence that her mother was a carrier. Unusual dominance of color-blindness in a heterozygous woman seems the more likely explanation. Kawakami cited a similar case.

As regards the distribution of color-blindness in the population, Garboe (1929) examined the whole population (451) of a little island in Denmark. He found 14 protanopes and 6 deuteranopes, all males, in 352 tested, or 5.7 per cent. The people have led an isolated life for centuries and are highly intermarried, yet the percentage of color-blindness has not been raised. On the other hand, there are "nests" of color-blindness in certain parts of Norway. These may have resulted from repeated mutation.

Many estimates of the frequency of color-blindness have been made, but they have generally been based on rather small numbers. In Europe and America they range from 1.2 to 8.2 per cent for males and 0 to 1 per cent for females. The Committee for Ophthalmological Research in England examined 14,846 persons and obtained a frequency of 4.16 per cent for males and 0.4 per cent for females. With the Ishihara color chart tests, however, this frequency is doubled. Thousands of recent tests for the navy (Vernon and Straker, 1943), using the Ishihara and Stilling charts, show in Great Britain a frequency of 7.5 per cent, including the color weak as well as the color blind. The frequency is 9.5 per cent in southwest England and only 5.4 per cent in northeast Scotland. They suggest that this may be associated with higher frequency of light hair and eyes in the north and east. Rivers (1901, 1905) found color-blindness, especially to blue, more frequent in the dark races. He attributed this to greater pigmentation of the macula lutea. Burt (1944) finds the correlation of color-blindness with dark hair to be 0.68 and with dark eyes 0.73. This could be due, not to genetic linkage but to a direct effect of pigmentation, or possibly to selective mating. Chebaxarov (1936) found in Russia the highest concentration of B blood group, the maximum frequency of protanomaly and the most conspicuous Uralo-Laponoid physical type in the vicinity of the Volga and Kama among Chuvash, Cheremiss and partly among the Tartars of Kasan, but this is apparently not a case of genetic linkage. Schiötz (1922) found 10.07 per cent color-blind males and 0.91 per cent color-blind females among 2005 ♂ and 2200 ♀ examined. Waaler (1927b) examined 9047 boys and 9072 girls in Norway, finding 8.01 per cent and 0.44 per cent color blind respectively. The latter figure does not differ statistically from the 0.64 per cent expected, which confirms that no selection is involved in connection with color-blindness.

Kilborn and Beh (1934) examined 2279 male Chinese students in Peiping and Chengtu and found 6.5 per cent color blind. They tested 1132 girls in Peiping and found an incidence of 1.7 per cent color blind.

Brunner (1930) found 8 per cent of men in Basel, Switzerland, color blind (5.75 per cent deuteranope, 2.2 per cent protanope). Waaler (1927) reckoned 14.72 per cent women carriers in the population, or one color-blind female to 34.23 carriers. Generally estimates have ranged from 4 to 8 per cent of affected men and about 0.4 per cent of women. Davenport (1930) has pointed out that large numbers have been examined only in the present generation, so there is no evidence as to whether the frequency of color-blindness is increasing. The percentages obtained naturally vary to some extent with the methods used. The Ishihara color charts are generally regarded as the most satisfactory. In a study of 3036 schoolboys in Basel, Switzerland, Wieland (1933) found 296 (9.7 per cent) color blind. They were distributed as follows:

Protanopes (P)	1.4%	2.2%
Extreme Protanopes (EP)	0.2%	
Protanomaly (PA)	0.6%	
Deuteranopes (D)	1.3%	5.8%
Extreme Deuteranopes (ED)	0.5%	
Deuteranomaly (DA)	4.0%	

Tests of color-blindness in chimpanzees (Yerkes, 1943) indicate that they are relatively insensitive to the red-yellow end of the spectrum.

Total Color-Blindness, Achromatopsia or Day-Blindness

This is a much rarer condition, sometimes called *monochromatic*[4] but more truly *achromatic vision*. Persons who are totally color blind see form without color, as in the twilight vision of normal persons. Everything appears in nuances of gray, with weak sight, nystagmus, nyctalopia (night blindness) and photophobia (sensitiveness to strong light). The condition appears, however, to be more like dazzling than true photophobia. The spectrum is also shortened at the red end.

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[4] In this extremely rare condition there is rod vision only (Pitt, 1944). A monochromat can match any color by any other color merely by the adjustment of their intensities.

The central vision is indistinct and there is frequently a scotoma (blind spot) in the middle of the field. There is blindness from sudden glare, as the mechanism for adapting the vision to light does not function. The condition of "total color-blindness" is therefore a wholly different thing from the various forms of color-blindness. It may be regarded as a reversion to an early vertebrate condition such as that of the fishes, which are believed not to perceive colors. The earliest supposed case was described by Huddart (1777) in a shoemaker. Two of his brothers were the same, while two other brothers, a sister and the parents all had normal vision.[5] This and later evidence shows that the condition is recessive, but recent work indicates that the gene crosses over between homologous parts of the X- and Y-chromosomes (see Chap. IV). An affected brother who was examined with striped ribbon, called light green yellow, he called orange green, and a tinge of red he called "a sort of blue."

Julia Bell (1926) recorded 119 cases in the world literature and Clements (1930) estimates the frequency as about 1 in 300,000 persons.

Peter (1926) made a study of total color-blindness in Switzerland. She found sixty families described in the literature since 1880. In fourteen of these blood-relationship of the ancestors was shown. One individual had one normal eye, the other affected. Vogt collected thirteen cases by following up the relatives of children with weak sight. Peter found eight families with sixteen cases and fifty normal siblings, which closely approaches the 1 : 3 ratio expected. Some of these pedigrees were extensive, being traced back through six or seven generations, all normal except the last generation. Aniridia is also present in one pedigree and partial color-blindness in another. Waardenburg (1928) found 19 cases in the Netherlands literature (9♂ 10♀), the sexes being equally affected.

Beach (1928) described a family in which three sisters showed achromatopsia, eight sibs being normal as well as the parents. This is in accord with a recessive inheritance, but the father had three brothers who were affected with pigmentary degeneration of the retina but had normal color perception. Two sisters of another family are mentioned who had the infirmity and called it *day blindness*. They were relieved by wearing very dark glasses. This condition is like one of permanent dark adaptation. Patients distinguish colors by their luminosity. In achromatopsia the greatest luminosity is in the green, while each of the types of color-blindness has its characteristic luminosity curve. For this reason, even total color-blindness is not certain to be detected by simple tests in color matching. Physicists call total color-blindness and normal dark vision *rod vision,* depending on the rods in the retina. Larsen (1921) found from sections of the eyes of the totally color blind that the cones of the fovea were short and plump instead of long and slender, so they presumably do not function. It had previously been assumed that they were absent. There may also be a cerebral defect. Pirenne (1944) finds that the rod-free area of the retina is best for color vision.

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[5] I formerly (Gates, 1929, p. 83) considered this a case of ordinary red-green color-blindness, but the account was somewhat uncertain and others have regarded it as achromatopsia. However, Dalton (1794) tested this family with about twenty colored ribbons, through an intermediary, and found the surviving affected son to be "exactly conformable" with himself. In Dalton's account there were six sons and one daughter, four of the sons affected.

In a physical study of color-vision defects, Pitt (1944) assumes three fundamental responses, B, G, R, which are stimulated in varying proportions by given stimuli. His results are in accord with the Young-Helmholtz theory of color vision. He believes that tritanopia is generally due to detachment of the retina, other cases being produced by jaundice, sclerosis of the lens or extremely dense macular pigmentation. Pickford (1945) cites a case of color-blindness in the left eye following an accident. He concludes that this negates all theories of color vision except that of Hering.

Shindo (1932) collected 78 cases of achromatopsia recorded in Japan and 103 in other countries, indicating that the condition may be much more frequent in Japanese. Sanders (1939) collected 18 families with 23 cases throughout Holland by asking for information from ophthalmologists. Some of these had already been studied by Waardenburg (1928). A typical pedigree is that of Maeda (cited from Komai, 1934[6]). As shown by Fig. 42, there are six cases in the fourth-fifth generation and the ancestors are much intermarried. Sanders gives three other

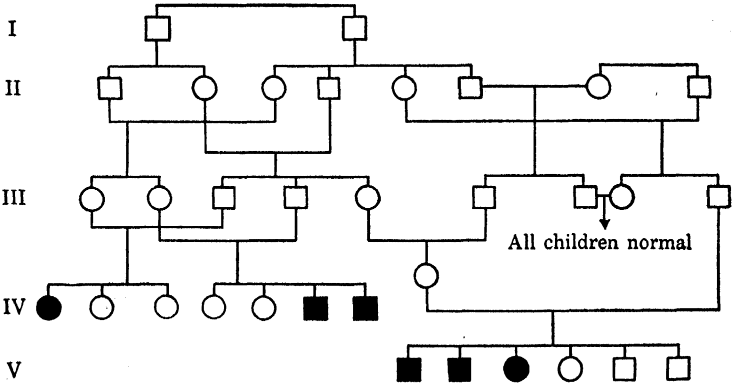

Fig. 42. Pedigree of total color-blindness. (After Maeda in Komai, 1934)

pedigrees, one of which goes back to common ancestors in the eighth generation. The sib frequency is found to be 22 per cent ± 5.86 for females and 24.3 per cent ± 7.05 for males, showing that the sexes are equally affected and a single recessive gene is involved. Geldard (1933) records the eleventh case in America. MacGillivray and MacLeod (1936) describe all the phenomena of total color-blindness in a boy of twelve. The parents were unrelated and it is very unlikely that there was any case in the family in the last three generations. It would be unsafe, however, to conclude that this is a mutation, as the condition has appeared after as many as eight generations of recessive inheritance in an inbred ancestry. The authors suggest that a defect of the visual centres of the brain may be involved.

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[6] One of the twenty-one pedigrees in Komai may be dominant.

Color-Blindness and Race

There are many records of the racial frequency of ordinary color-blindness, some of which may be referred to here as well as the view, partly based on philology, that the color sense of civilized man has become more intense within historical times. Table 11 gives the frequency of color-blindness in various races.

TABLE 11

FREQUENCY OF COLOR-BLINDNESS IN DIFFERENT RACES

	Number	*Frequency*	*No. ♀♀*	*%*	*Author*
Europeans	3734	8.04%			Clements 1930
Indians in S. W. States	624	1.9 %			Clements 1930
American Negroes	325	3.7 %			Clements 1930
Full-blood Indians	392	2. %			Clements 1930
American Negroes	1628	3.75%	651	0	Crooks 1934
American Negroes	2019♂	3.91%	—	—	Crooks 1936
American Negroes			722	0.14	Crooks 1936
American Negroes (Southern)	538♂	3.9 %	496	0.8	Garth 1933
American Negroes (Northern)	254♂	2.8 %	165	0	Garth 1933
Indians	562♂	2.5 %	337	0.0	Garth 1933
Navajo	535♂	1.1 %	456	0.7	Garth 1933
Whites	795♂	8.4 %	232	1.3	Garth 1933
Jews	200♂	4.0 %	175	0	Garth 1933
Chinese students	1115♂	6.3 %	—	—	Kilborn & Beh (1934)
Chinese students	1164♂	6.9 %	1132	1.7	Chang 1932
Todas	320♂	12.8 %	183	1.1	From Clements 1930
Lapps	158♂	6.3 %	111	0.9	From Clements 1930
Eskimo	125	0.8 %	—	—	From Clements 1930
Bechuana (S. Africa)	407♂	3.4 %	574	0.35	Squires 1942

The Ishihara charts, consisting of a number in one color on a background of another color, were used in all the tests.

From these and similar results it can be seen that whereas color-blindness runs about 8 per cent in white males and 1 per cent in white females, it is only about 1 to 2.5 per cent for male Indians, 4 per cent for male Negroes and 6 to 7 per cent for male Chinese. The Todas, a pastoral people of South India, are extraordinarily high with nearly 13 per cent, the Lapps appear intermediate (from the few tested), while color defect seems rare in the Eskimo. The racial significance of such results remains to be appraised. Squires (1942) found that in the Bechuanas 12 per cent of the men and 9 per cent of the women were unable to distinguish between gray and green; 4 per cent of men and 5.4 per cent of women could not distinguish purple from violet. Their languages were also poor in color terms, which are evidently only developed in any language as they are needed for particular purposes. Among 981 Bechuanas 3.4 per cent of the males and 0.35 per cent of the females were color blind. Fry (1935) found no color-blind Australian aborigines. In one test, fifty traced Stilling's color plates correctly.

Obermaier (1924) states that red and yellow ochre have been found in the most ancient Mousterian (Paleolithic) deposits. The cave art of Late Paleolithic times included representations in colors, which included black (carbon or manganese ore), light and deep yellow, orange, red, reddish gray, violet and terracotta all made from ochre. White occurs rarely but blue and green are altogether unknown. This with other evidence of primitive and ancient man makes it seem likely that Paleolithic man was unable to discern green and blue, and possibly the whole short-wave end of the spectrum, although violet was among the pigment colors he used.

The unsatisfactory character of the color terms in the classical languages for scientific purposes is well known. Gladstone showed the vagueness of Homer's color terminology and concluded that the people of that age could do little more than distinguish differences in brightness, yet the prehistoric Egyptians had blue and green beads before the time of Homer. Some of the following facts have been taken from the discussion by Clements (1930) of the color sense in primitive man. From a study of ancient Greek literature, the Indian Vedic hymns, the Zendavesta, Norse Eddas and ancient Chinese and Semitic writings, Geiger concluded that red vision evolved first, then yellow and green, finally blue. Magnus collected evidence from various primitive peoples whose language showed the same color poverty as the ancient literatures. Rivers (1901) showed that the Australian aborigines lumped the colors together. Red, purple and orange they called *oti;* white, yellow and green, *yopa;* black, blue, indigo and violet, *manara.* Some tribes applied names to green and yellow. Among the Kiwai Papuans, few had a special name for green. Blue, black and violet were considered the same. On Murray Island in Torres Straits there was no word for blue as distinct from black, while on another island the terms for blue and green were sometimes interchanged. Tests with the Lovibond tintometer showed a degree of insensitiveness to blue color, which was associated with the vague nomenclature, but extreme sensitivity to the red. Bartlett (1929) similarly finds no native Malay word for blue. Red, yellow and green have specific terms; but the words for orange and violet are indefinite and not widely used, while Batak lacks words for these colors. The same word does for light blue and green, and for dark blue and black. Thus the philological method leads to consistent results, the evolutionary sequence being red ⟶ yellow and green ⟶ blue.

Racial differences in color perception may depend partly on pigmentation. The macula lutea of the retina, which is the region of most distinct vision, is pigmented with reddish-yellow. Hence the blue and green rays are more strongly absorbed there. There is reason to think that the macula of the dark races is more strongly pigmented. If so, the blue and green would be more strongly absorbed, resulting in less sensitiveness than to the red and yellow.

Rivers recognized four stages in the evolution of color language: (1) Only red was recognized apart from white and black. (2) There were terms for red and yellow, but green was indefinite. (3) Terms existed for red, yellow and green, but blue was borrowed from English. (4) There were terms for both green and blue but they tended to be confused. According to Rivers, there is no word for blue in Welsh, Chinese or Hebrew. It is lumped either with black or with green. The Eskimos, on the other hand, have a highly developed color sense. They call purple bluish-red and violet reddish-blue. Homer's color vocabulary was in the same early stage of development as that of primitive modern languages.[7]

Rivers tested 150 natives of Murray Island and found no case of color-blindness or confusion of red and green there or in Australia, but he found 3 cases of red-green color-blindness among 8 natives tested in the Loyalty Group.

Eldridge-Green (1911) concluded that perception of the spectrum began with only brightness discrimination, then red was distinguished from violet, then green was recognized, then orange-yellow and finally blue, followed by the separation of orange from yellow and lastly indigo. According to Mrs. Ladd-Franklin's theory of color vision, the evolution of the color sense took place in three stages: (1) White, black and gray were discriminated, (2) yellow and blue, (3) red and green. These correspond to color zones of the normal retina, the outer zone seeing only colorless tones, the middle zone seeing blue and yellow, the central area red and green. According to this theory, a mixture of red and green gives yellow because the eye reverts to the old response before red and green were differentiated. If this theory is true, blue-yellow color-blindness should not occur in the absence of red-green color-blindness, but it does so although the condition is extremely rare. On this theory also red-green color-blindness should be very common in such native peoples as the Australians, yet it apparently does not occur. Nevertheless, a very large number of human abnormalities can be most reasonably interpreted as reversions or a failure to complete development, and probably this is in some sense true of the genes for color-blindness. Since there are six genes, however, at two loci of the X-chromosome, not counting the genes for blue-yellow defect and for total color-blindness, it seems clear that they will not fit into any phylogenetic series. Among animals it appears that cats and dogs are totally color blind, pigeons see the red end of the spectrum best, fowls see blue but not violet, while bees see blue but not red although they also see the ultraviolet.

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[7] It should be pointed out that some writers claim that a deficient color vocabulary in any race is no indication that it is lacking in color sensitivity.

Dunlop and Loken (1942) claim that red color-blindness is not a simple sex-linked Mendelian character but that it can be "cured" by administration of large doses of vitamin A (25,000–50,000 units per day). While it may well be true that color-blindness can be temporarily overcome by administration of very large doses of vitamin A, this in no way alters the fact or the method of inheritance and such claims are made only by those who lack an understanding of the mechanisms of heredity. Since this was written, Elder (1943) has shown that these claims are unfounded.

LITERATURE

Baetjer, Anna. 1929. Case of a totally color-blind female. *Eugen. News* 14:6.

Bartlett, H. H. 1929. Color nomenclature in Batak and Malay. *Papers Mich. Acad. Sci., Arts and Letters* 10:15–38.

Beach, S. J. 1928. Total congenital color-blindness. *J. Am. Med. Assoc.* 91:934–938.

Bell, Julia. 1926. Colour-blindness. *Treas. of Human Inher.* Vol. II, part 2, 125–267. Pls. 15.

Bowditch, H. 1922. Red-green color-blindness in three allied families. *J. Hered.* 13:139–142.

Brunner, W. 1930. Über den Vererbungsmodus der verschiedenen Typen der angeborenen Rotgrünblindheit. *Graefe's Arch. f. Ophthal.* 124:1–52.

Burt, C. 1944. *Man* 44:79–80.

Chang, S. P. 1932. Statistics on color-blindness among students in Peiping. *Nat. Med. J. China* 18:806.

Chebaxarov, N. 1936. Blood groups and colour blindness in Comi. *Anthrop. Zhurnal* 396–413.

Clark, W. E. L. 1940. Anatomical basis of colour vision. *Nature* 146:558–559.

Clements, F. 1930. Racial differences in color-blindness. *Am. J. Phys. Anthrop.* 14:417–432.

Cole, L. J. 1919. An early family history of color-blindness. *J. Hered.* 10:372–374.

Crooks, K. B. N. 1934. On the incidence of color-blindness among negroes. *Science* 80:269.

———. 1936. Further observations on color-blindness among negroes, with genealogic and geographic notes. *Hum. Biol.* 8:451–458.

Cunier, F. 1839. Observation curieuse d'une achromatopsie héréditaire depuis cinq générations. *Ann. d'Oculistes* 1:417–420.

Dalton, John. 1794. Extraordinary facts relating to the vision of colours. *Mem. & Proc. Manchester Lit. & Phil. Soc.* 5:28–45.

Davenport, C. B. 1930. Sex linkage in man. *Genetics* 15:401–444.

Döderlein, G. 1922. Über die Vererbung von Farbensinnstörungen. *Arch. f. Augenhlk.* 90:43–66.

Dunlop, K. & Loken, R. D. 1942. Vitamin A for color-blindness. *Science* 95:554.

Elder, J. H. 1943. Effectiveness of vitamin A in the treatment of defective color vision. *Science* 97:561–562.

Eldridge-Green, F. W. 1911. Color-blindness and color perception. *Lancet* i. 285–290.

Engelking, E. 1926. Die Tritanomalie, ein bisher unbekannter Typus anomaler Trichromasie. *Arch. f. Ophth.* 116:196.

Franceschetti, A. 1928. Die Bedeutung der Einstellungsbreite am Anomaloskop für die Diagnose der einzelnen Typen der Farbensinnstörungen, nebst Bemerkungen über ihren Vererbungsmodus. *Schweiz. Med. Wochens.* 9:1273–1279.

Fry, H. K. 1935. Aboriginal mentality. *Med. J. Australia.* 1:353–360.

Garboe, Axel. 1929. Studien über eine kleine, endemische Bevölkerung in Dänemark. *Genetica* 11:465–490.

Garth, T. R. 1933. The incidence of color-blindness among races. *Science* 77:333–334.

Geldard, F. A. 1933. A case of congenital total color-blindness. *J. Opt. Soc. Amer.* 23:256.

Gowen, J. W. 1933. Anomalous human sex-linked inheritance of color-blindness in relation to attached sex-chromosomes. *Hum. Biol.* 5:130–134.

Haldane, J. B. S. 1932. Genetical evidence for a cytological abnormality in man. *J. Genet.* 26:341–344.

Holmes, G. 1945. The organization of the visual cortex in man. *Proc. Roy. Soc.* 132B:348–361. Figs. 6.

Horner. 1876. Ein Beitrag zum Vererbungsgesetz. Bericht über die Verwaltung des Medizinwesens des Kanton Zürich von Jahre 1876.

Huddart, Joseph. 1777. An account of persons who could not distinguish colors. *Phil. Trans. Roy. Soc.* 67:260–265.

Just, G. 1925. Zur Vererbung der Farbensinnstufen beim Menschen. *Arch. f. Augenhlk.* 96:406–418.

Just, G. 1934. Faktorenkoppelung, Faktorenaustausch und Chromosomenaberrationen beim Menschen. *Ergeb. der Biol.* 10:566–624.

Kilborn, L. G. & Beh, Y. T. 1934. The incidence of color-blindness among the Chinese. *Science* 79:34.

Larsen, H. 1921. Demonstration mikroskopischer Präparate von einem monochromatischen Auge. *Zeits. f. Augenhlk.* 46:228.

Levit, S. G. & Serebrovsky, A. S. 1929. *Med. J. Biol.* (Russian).

Little, C. C. & Gibbons, M. 1921. Evidence for sex-linked lethal factors in man. *Proc. Soc. Exp. Biol. & Med.* 18:111–115.

Lort, Michael. 1779. An account of a remarkable imperfection of sight. *Phil. Trans. Roy. Soc.* 68:611–614.

MacGillivray, A. M. & MacLeod, A. S. 1936. Congenital total colour-blindness. *Lancet* 231:626–627.

Martin, L. C. & Wright, W. D. 1935. Med. Research Council, *Special Report Series*, No. 200. Pp. 58.

Maxwell, J. Clerk. 1855. Experiments on colour, as perceived by the eye, with remarks on colour-blindness. *Trans. Roy. Soc. Edinb.* 21:275–298. Pl. 1.

Meyer, H. 1932. Ueber den Gelb-Blausinn der Protanopen und Deuteranopen im Vergleich mit dem der normalen Trichromaten. *Klin. Monatsbl. Augenhlk.* 88:496–507.

Morgan, L. V. 1922. Non-criss-cross inheritance in *Drosophila melanogaster. Biol. Bull.* 42:267–274.

Nelson, J. H. 1938. Anomalous trichromatism and its relation to normal trichromatism. *Proc. Phys. Soc. Lond.* 50:661–702.

Nettleship, E. 1906. Cases of colour blindness in women. *Trans. Ophth. Soc. U. K.* 26:251–258.

Obermaier, H. 1924. *Fossil Man in Spain.* Yale University Press. Pp. 495.

Oloff, H. 1935. Ueber angeborene blauanomale Trichromasie (Tritanomalie). *Klin. Monatsbl. f. Augenhlk.* 94:11–20.

Peter, Lina. 1926. Zur Kenntnis der Vererbung der totalen Farben blindheit mit besonderer Berücksichtigung der in der Schweiz bis jetzt nachgewiesenen Fälle. *Arch. J. Klaus-Stift.* 2:143–189. Figs. 5.

Pickford, R. W. 1944. Women with colour-blind relatives. *Nature* 153:409.

———. 1945. Colour blindness in left eye following an accident. *Nature* 155:336–337.

Pirenne, M. H. 1944. Rods and cones and Thos. Young's theory of colour vision. *Nature* 154:741.

Pitt, F. H. G. 1944. Monochromatism. *Nature* 154:466–468.

———. 1945. The nature of normal trichromatic and dichromatic vision. *Proc. Roy. Soc.* 132B:101–117.

Pole, W. 1893. Data on the phenomena of colour-blindness, chiefly derived from foreign sources. *Proc. Roy. Soc. Edinb.* 20:103–140.

Rath, B. 1938. Rotgrünblindheit in der Calmbacher Blutersippe. Nachweis des Faktorenaustauschs beim Menschen. *Arch. f. Rass. Ges. Biol.* 32:397–407.

Rivers, W. H. R. 1901. Primitive color vision. *Pop. Sci. Mon.* 59:44–58.

Rivers, W. H. R. 1905. Observations on the senses of the Todas. *Brit. J. Psychol.* 1:321.

Sanders, J. 1939. Die Erblichkeit bei totaler Farbenblindheit. *Genetica* 21:280–284.

Schinz, H. R. 1941. Ergebnisse der physiologischen Genetik in ihrer Bedeutung für die menschliche Erbforschung. *Arch. J. Klaus-Stift.* 16:645–668. Figs. 5.

Shindo. 1932. *Acta Soc. Ophthal. Japon.* (Cited by Sanders).

Schiötz, I. 1920. Colour-blind females: the inheritance of colour-blindness in man. *Brit. J. Ophthal.* 4:345–359, 393–403.

———. 1922. Rotgrünblindheit als Erbeigenschaft. *Klin. Monatsbl. f. Augenhlk.* 68:498–526.

Schmidt, I. 1934. Ueber manifeste Heterozygotie bei Konduktorinnen für Farbensinnstörungen. *Klin. Monatsbl. Augenhlk.* 92:456–467.

Sedgwick, W. 1861. On sexual limitation in hereditary disease. *Brit & Foreign Med.-Chirurg. Rev.* 27:477–498, 28:198–214.

Sheppard, S. E. 1945. The physical chemistry of color vision. *Science* 102:207–208.

Siemens, H. W. 1926. Eine prinzipiell wichtige Beobachtung über die Vererbung der Farbenblindheit. *Klin. Mbl. Augenhlk.* 76:769–776.

Squires, B. T. 1942. Colour vision and colour discrimination, amongst the Bechuana. *Trans. Roy. Soc. S. Afr.* 29:29–34.

Stilling, J. 1878. Blau-Gelbblindheit mit unverkürztem Spectrum. *Centralbl. f. prakt. Augenhlk.* 2:99–100.

Trendelenburg, W. & Schmidt, J. 1935. Untersuchungen über Vererbung von angeborener Farbenfehlsichtigkeit. *Sitzungsber. d. Preuss. Akad. Wiss., Phys-Math. Kl.* 13–81.

Vernon, P. E. & Straker, A. 1943. Distribution of colour-blind men in Great Britain. *Nature* 152:690.

Vogt, T. 1922. Über geschlechtsgebundene Vererbung von Augenleiden. *Schweiz. Med. Wochens.* 52:77–83.

Vogt, T. & Klainguti, R. 1922. Weitere Untersuchungen über die Entstehung der Rotgrünblindheit beim Weibe. *Arch. f. Rass. u. Ges. Biol.* 14:129–140. Figs. 6.

Waaler, G. H. M. 1927a. Über die Erblichkeitsverhältnisse der verschiedenen Arten von angeborener Rotgrünblindheit. *Acta Ophthal.* 5:309–345.

———. 1927b. Über die Erblichkeitsverhältnisse der verschiedenen Arten von angeborener Rotgrünblindheit. *Zeits. f. Abst. u. Vereb.* 45:279–333.

Waardenburg, P. J. 1928. Over totale kleurenblindheid en den waargenomen toestand van de gele vlek. *Sitz. ber. Neder. Oogh. Gez. Ned. T. v. Gen.* 72. II. 49.

———. 1935. Vererbungsergebnisse und -probleme am menschlichen Auge. *Zeits. f. Abst. u. Vererb.* 70:358–376.

Wald, G. 1945. Human vision and the spectrum. *Science* 101:653–658.

Wieland, Max. 1933. Untersuchungen über Farbenschwäche bei Konduktorinnen. *Graefe's Arch. f. Ophthal.* 130:441–462.

Wilson, E. B. 1911. The sex chromosomes. *Arch. Mikr. Anat.* 77: Part II, 249–271. Figs. 5.

Wölfflin, E. 1923. Über das Vererbungsgesetz der anomalen Trichromaten. *Pflüger's Arch.* 201:214–219.

Yerkes, R. M. 1943. *Chimpanzees, a Laboratory Colony.* Yale Univ. Press. Pp. 321, pls. 63.

Chapter VII

HEREDITARY VARIATIONS AND ABNORMALITIES OF THE EYE

PREVIOUS chapters have considered eye color and color-blindness from the genetical and anthropological points of view. This chapter will deal with some racial differences and with abnormalities of the eye. Duke-Elder (1940), in his textbook of ophthalmology, gives a number of pedigrees of abnormalities.

The racial differences, apart from eye color, are concerned mainly with the eyelids and especially with what is commonly called the *Mongolian fold* and the epicanthus. The upper eyelid develops in two parts, an inner and an outer. Occasionally a notch (coloboma) remains at the point of union. Aichel (1932) has made a classification of the various types of eyefold found in different races, which have not previously been clearly distinguished. Only the main differences need be entered into here. The folds are classified as orbital, palpebral, tarsal and marginal. It is claimed that the epicanthus or plica orbitalis may be inner (by the nose), median or (rarely) outer (epicanthus lateralis, Fig. 43). Figure 44 represents the epicanthus medialis of a German woman, extending from the nasal fold into the upper eyelid. The epicanthus nasalis is not uncommon as a temporary structure in children of all human races. Barbosa Sueiro (1931) described a family in Lisbon with epicanthus lateralis present in four generations, predominantly in the females.

Plicae palpebralis are folds of the eyelid, which may take several different forms. Figure 45 shows the Mongolian fold in a girl of eleven of German-Polish descent. This type of fold is not very uncommon in European children, but generally disappears later. In closed eyes the epicanthus is visible (Fig. 44), while the Mongolian fold is not. Figure 46 shows the Hottentot fold in the median and lateral part of the upper lid. Figure 47 shows the Indian fold (plica naso-marginalis) in an Indian girl of Bolivia. Figure 48 is a Hottentot woman with a combination of the Mongolian fold and the Indian fold. The

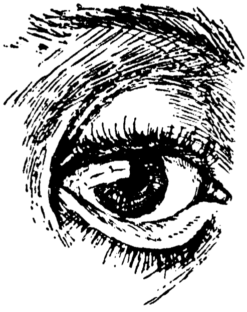

Fig. 43. Epicanthus lateralis in right eye. (From Aichel after Löhlein)

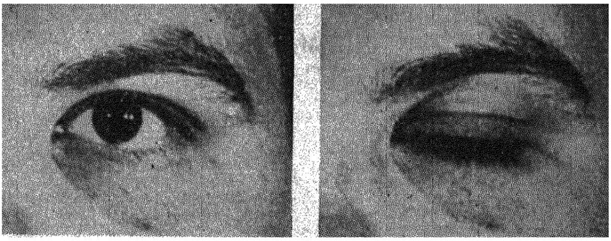

Fig. 44. Epicanthus medialis of a German woman, eye open and closed. (After Aichel)

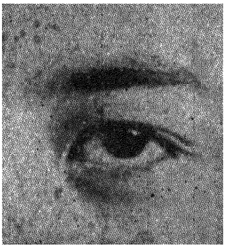

Fig. 45. Mongolian fold in a girl of 11 of German-Polish descent. (After Aichel)

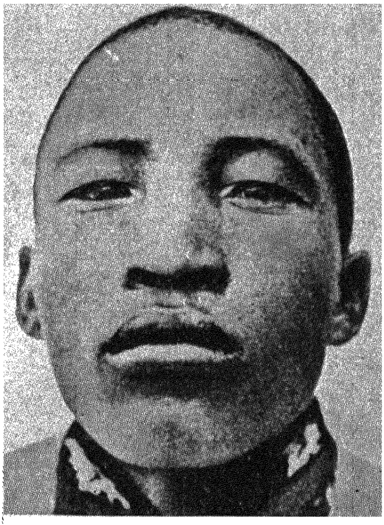

Fig. 46. Rehoboth hybrid with Hottentot fold — median and lateral overhang of upper lid. (After Fischer)

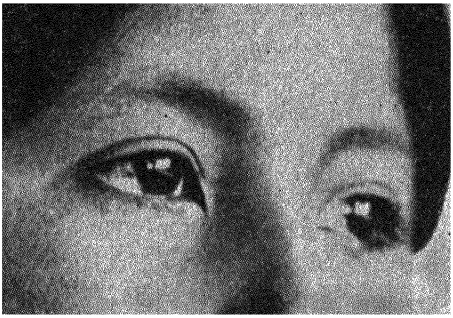

Fig. 47. Plica naso-marginalis in a 13-year-old Indian girl of Bolivia — Indian fold. (After Aichel)

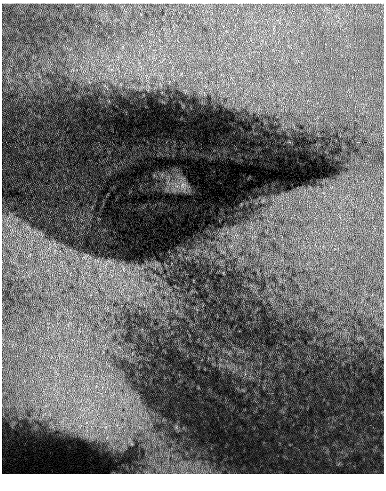

Fig. 48. Hottentot woman with a combination of the Mongolian and the Indian eyefold. (After Aichel)

Negro eyefold (Fig. 49) or plica malo-marginalis, is one in which the upper lid at the outer angle of the eye crosses over the lower lid.

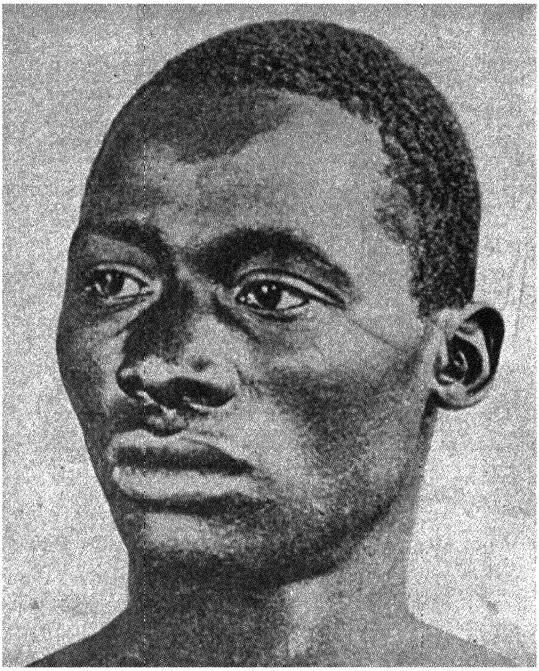

Fig. 49. Negro eyefold or plica malo-marginalis. (After Aichel)

The same condition is shown in a German woman in Fig. 50. It frequently occurs in Europeans past middle age. From twin studies, Bühler (1940) claims to find four forms of *plica orbito-palpebralis*, which he concludes are inherited, but they cannot be distinguished in his photographs.

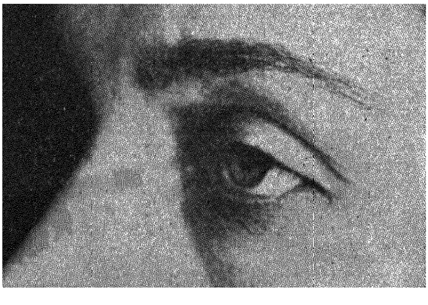

Fig. 50. Plica malo-marginalis in a German woman. (After Aichel)

It will be appreciated that the muscles involved differ in these various conditions, which are therefore distinct. Each may be inherited as a unit as appears to be true of certain body muscles, but there is very little evidence on this point. Several of them have been confused together under the general name of *Mongolian fold*. According to Aichel, the epicanthus is generally found in African children while in Europe the children more frequently have the Mongolian fold. The original form of the Chinese symbol for the eye shows that the epicanthus and Mongolian fold were both present in the Chinese at least as early as 1500 B C.

Wen (1934) made a study of the development of the Mongolian fold in Chinese and white foetuses. He found a fold highly placed on the external surface of the upper eyelid in all whites from the twenty-fifth week and in one Chinese. A much lower fold was present in all Chinese from the twenty-second week. The Chinese fold is thicker, due to (*a*) the lower marginal fibres of the orbicularis oculi muscle being disposed backward in a curve, (*b*) an extension of the tendon fibres of the levator palpebrae superioris muscle ending in the marginal lid fold, (*c*) deposition of fat in the central subcutaneous connective tissue. Fortuyn (1932) says that the epicanthic fold is a single recessive genic difference and gives further details of the anatomy. Hildén (1938) showed that the Mongolian fold varies with age. After twenty years it gradually disappears and is rare in mongoloids over 40 years of age. Among Kalmucks and Torguts under 25 years of age, 95 per cent had the eyefold, between 25 and 29 years the figure was 42 per cent, and over 30 years 37 per cent.

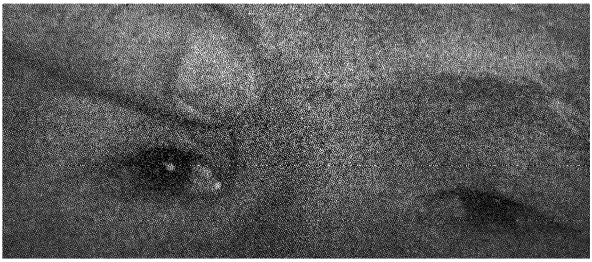

Fig. 51. Epicanthus and Mongolian fold in a Korean. (After Chouke)

Chouke (1929) has shown that the incidence of the epicanthus decreases among Caucasian children as age increases. He mistakenly suggests that the terms *epicanthus* and *Mongolian fold* should be used interchangeably, but the former extends in the main vertically and is associated with a flattened root of the nose and a very small superciliary arch while the latter extends laterally and is a fold more or less completely enclosing the eyelashes, only the tips of which project. Metschnikoff regarded the condition as an arrested development. Figure 51 shows the presence of both in a Korean man. The Mongolian eye differs also in being almond-shaped rather than oval, i.e., having a narrower palpebral fissure than a European. In various races the angle at which the orbit is set in the head also differs markedly. A superabundance of skin around the root of the nose may be a factor in the epicanthus in Caucasian children. It appears that when the Mongolian fold and the epicanthus are both present in a Caucasian infant the fold generally disappears first while the epicanthus may persist into childhood. Keith (1923) states that the epicanthic fold (which appears to include both the epicanthus and the Mongolian fold) is represented in the foetal stage of all races. Waardenburg (1930) found it present from the beginning of the third to the beginning of the sixth month, but not covering the canthus. Bolk (1929), without distinguishing the various types, finds that an epicanthic fold persists in Mongols, Negroes, Malayans — and even in whites through pathological retardation in the so-called Mongolian idiot. Among newborn in southern Germany a more or less developed epicanthus is not at all rare, and the same appears to be true of other Caucasians.

Lange (1936) regards deep-set or prominent eyes as racial characters, the former found in the Nordic and the latter in the East Baltic race. Apart from abnormally prominent eyes, as in Basedow's disease, he shows that eyes may change in the individual from deep-set in youth to prominent in middle life, or vice versa. The inheritance element behind these differences is unknown.

Routil (1933) studied the *oblique eye* and recognizes three genetic factors related to this condition. Mongolians mostly have the factor **a**, producing a strongly oblique eye with the outer end above and the inner end below the horizontal; **h** produces the horizontal eye generally found in Caucasians. Negroes frequently show **i** as well as **a** and **h**. In **i** the inner end of the eye is above and the outer end below the horizontal. Routil finds **a** more frequent in women, **i** in men, **a** being more infantile. From many pedigrees it is seen that **h** × **h** gives only **h** and **a** × **a** only **a**, whereas **h** × **a** may give **h** or (**a**),[1] **i** × **h** gives (**a**) or **h** (sometimes one eye of each type), and (**i**) × (**a**) gives (**a**) or **h**. The matter requires further analysis. In examining 3000 W. African negroes (children and soldiers), Scott (1945) found that 90 per cent had pigment spots in the conjunctiva and all had a ring of pigment at the corneo-scleral junction. There were five cases of flocculi iridis and congenital lens changes were rare. The fundus was red, not chocolate or slate-gray in color.

Trichomegaly or long eyelashes (22 mm.) are recorded by Gray (1944) as a family character.

An exhaustive monograph on hereditary *abnormalities of the eye* has been published by Waardenburg (1932). References not given here may be found there, but important papers subsequent to 1932 are cited here.[2]

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[1] Weak **a**.

Ptosis (drooping of the eyelid owing to paralysis of its muscles) is a condition of which there are many pedigrees, and it is often associated with *Epicanthus*. It occurs in all grades, sometimes only producing a sleepy appearance, but in others the head has to be thrown back to see. It is not always inherited, but may be caused by an injury or by paralysis of the third nerve. It is due to absence or impairment of the levator palpebrae superioris muscle which raises the eyelid. Usually at least, it is dominant in inheritance. One case is cited by Macklin (1927a) of a man with normal parents who had four children showing ptosis. This might be explained as a mutation, or more probably as indicating that the defect was a conditioned dominant in this pedigree. Briggs (1918, 1919) described a pedigree of six generations from a woman having this defect. The lineage belongs to a family in the mountains of the southern states, and includes 128 individuals, half of whom have the defect. Photographs are given, and a chart indicating that the character is dominant. Flieringa (1924) describes a family in which the mother was unable to lift the eyelids very far. Her ancestors were quite free from the condition so far as could be traced, as was also the father and his ancestors. Yet all the children of both sexes exhibited the defect. This would appear to be a *de novo* origin of ptosis and its inheritance as a dominant in the children. Weissenberg (1927) gives a pedigree showing ptosis on the left side only, inherited as a dominant (eight cases) in three generations of a Russian family in Baku. In a later paper (1928) he describes a Jewish family in the Ukraine in which it is an irregular dominant varying (4 cases ♂) from weak expression in the left eye to strong expression in both eyes.

A pedigree combining epicanthus with ptosis was described by Usher (1925). Following von Ammon (1831) he distinguishes (1) epicanthus supraciliaris bilateralis, in which the skin fold originates in the eyebrows and extends down toward the tear sac or the nostrils,

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[2] It is not without interest that even Galen (A.D. 130–201) had some idea of inheritance in connection with conditions of the eye. His work on the eye, *De Usu Partium*, Book X, was preserved by being translated from Greek into Arabic by the great Arabic physician, Hunain, in Baghdad. An English translation from the Arabic is published by Meyerhof (1928). This work contains several diagrams, but Galen's mistakes, such as placing the lens in the centre of the eye, were all repeated. The function of the retina was unknown, but it is stated that both dilation and dislocation of the pupil may be either "natural" or accidental in origin. Lagophthalmos can be congenital or result from unskilful sewing up of the lids. Myopia, hyperopia and nyctalopia were recognized and the treatment for night-blindness included anointing the eye with the juice from roasted goat's liver and eating the liver. Much space is devoted to operations for cataract, but there is no indication that its inheritance was recognized, although various forms were described.

(2) E. palpebralis, from high in the upper lid to the lower margin of the orbit, and (3) E. tarsalis, which originates in the tarsal fold of the upper lid and loses itself in the skin close to the inner canthus. Such a fold, uniting the upper and lower lids at the inner angle of the eye, is normal in the Mongolian race and occurs with varying frequency in related races. Epicanthus is stated to occur in about half the cases of Mongolian idiocy. It is similar to the plica marginalis of mongoloids. Evidently in adults it represents a failure to complete development. In only one pedigree does epicanthus apparently occur without ptosis. In Usher's pedigree a man with both had seventeen similar cases in his descendants in three generations. The inheritance is that of a strict dominant, except in one case where it skipped a generation and another in which two generations were skipped; but the individual in the former case had ptosis on one side only, and in the latter case (IV. 4) epicanthus without ptosis.

Manson (1928) cites a family in which the father, two daughters and a son have epicanthus with ptosis, one girl being normal. They have to throw back their heads or raise their brows to see. A similar family, known as the *slit-eyed people*, and probably with a combination of epicanthus and ptosis, is described from the mountains of Georgia (Stuckey, 1916). Its members had constricted eyelids, dominant in four generations. The badly constructed pedigree of Ross (1932) contained 7 cases (3♂ 4♀) in four generations. He states that incomplete development of the nasal bones is the main factor in its production.

In a later paper, Usher (1935a) points out that persons with epicanthus alone are usually unaware of any anomaly. In the population of Munich, Martin found it in 33 per cent of infants of one to six months, in 25.5 per cent of infants seven to eleven months; at three to six years it was present in 14 per cent of boys and 5 per cent of girls, at twelve to twenty-five years in 3.3 per cent of males and 2.6 per cent of females. In a large published pedigree of epicanthus (Meirowsky, 1926) it is dominant, 32 cases (20♂ 12♀) in five generations. Usher finds in all pedigrees, of which he contributes twenty-two, 180 cases (89♂ 81♀). This tendency in Caucasians toward the persistence of a condition which is a racial character in Mongolians, is evidently inherited in different degrees and in some families is a somewhat irregular dominant. One pedigree appears recessive.

Ptosis with epicanthus is the usual condition and was found by Usher in 26 pedigrees with 175 affected members (105♂ 62♀). The inheritance is dominant with an occasional skip. As shown in Fig. 52, the palpebral fissure is not only narrowed to 2 mm. from 10–15 mm., but also shortened from *ca.* 30 mm. to 20–22 mm. In Japanese the normal width is 8.8 mm. Vignes (1889) published an early pedigree with 12 cases (9♂ 3♀) in four generations. The second generation of this family had been observed by Sichel in 1845. Biro (1934) describes a family in which the grandmother, two sons and one daughter and eleven grandchildren (male) were all affected, but females of the third generation were unaffected. One grandson had also paralysis of the upper and lower rectus muscle together with strabismus (squint) and nystagmus.

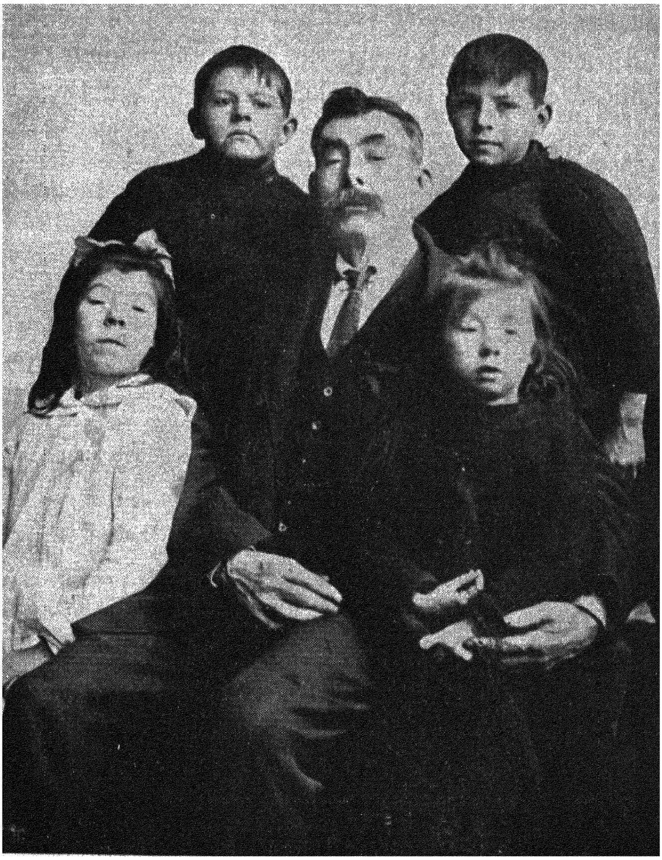

Fig. 52. Ptosis and epicanthus in father and two of four children. (After Usher)

Ptosis without epicanthus generally shows loss of movements of the eyeball. The upper eyelid is raised by the levator palpebrae superioris and Müller's palpebral muscle. The former is innervated by the oculomotor (3rd cranial) nerve, the latter by fibres from the cervical portion of the sympathetic trunk. Paralysis of either nerve causes ptosis, but there is only a slight droop (Horner's syndrome) when the sympathetic fibres are cut, as shown by experiments on monkeys. The McIlroy (1929) pedigree contains 12 cases (7♂ 5♀) in four generations. The pedigree is very incomplete, as there is no account of the children of affected females. Ptosis and epicanthus must be very closely linked, or possibly the result of a single gene. This paper and that of Usher give some evidence of possible linkage with brown eyes and hair. The usual presence of strabismus and nystagmus in these pedigrees raises the question of their genetic basis in such families. Are they also linked genes or are they secondary phenomena? Rodin (1936) described a family with dominant hereditary ptosis in one eye only. Either eye may be affected. In a second family three children out of six were bilaterally affected, but there were no others in the family with any ocular defect. Cockayne's (1931) pedigree is not true ptosis from drooping of the upper eyelid, but is due to a short palpebral fissure which prevents wide opening of the eyes (Fig. 53). There is not true epicanthus, but a fold from the under lid overlaps the upper. This family condition has been inherited for many generations. The last five generations show 15 known cases (12♂ 3♀), the sibships numbering 13 affected: 14 normal.

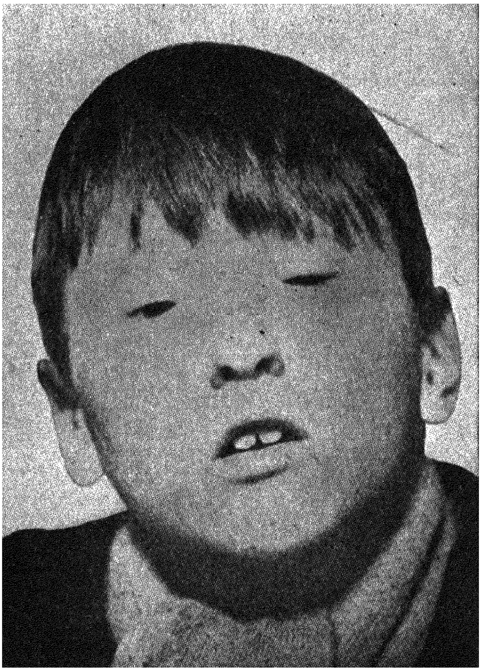

Fig. 53. Short palpebral fissure and bicanthus. (After Cockayne)

Forty-four pedigrees of ptosis are known, with a total of 211 cases (93♂ 106♀). The excess of females is the reverse of the condition in ptosis with epicanthus. The transmission was thirty-six times through the female and thirty-one times through the male, whereas in ptosis with epicanthus it is only seven times through the female and thirty-nine times through the male. The genetic relation between these two conditions remains obscure. It is perhaps one of close linkage, since it would be unusual for a single gene in one pedigree to produce the same conditions as two different genes in others. But compare syndromes (Chap. XVIII). The apparently greater frequency of ptosis can be accounted for by its easier recognition. In Dollar's (1938) family the ptosis is not congenital but makes its onset in each case at about fifty years of age. Grandmother, mother, two sons and a daughter were affected. She cites an earlier pedigree in which the onset was always at fifty. Meumann (1928) also described a dominant pedigree of non-congenital ptosis.

Giri (1944) cites a family in which the mother had bilateral ptosis, the father, oblique eyes. One of three sons had both conditions together with a left hand having digits I and II fused, III and IV absent, V (and probably II) having only two phalanges.

Horner's syndrome, discovered in 1869, is a mild form of ptosis. It occurs when some portion of the cervical part of the sympathetic nervous system is subjected to disease or trauma, accidental or surgical, and is sometimes associated with heterochromia iridis and the Argyll-Robertson sign.

Under the name ptosis Dimitry (1921) describes a condition in a Sicilian family which he says is really *blepharophimosis* (narrowing of the slit between the eyelids). There were 21 cases (7♂ 11♀ 3 unknown) in five generations, the inheritance strictly dominant, but the sibships numbered 20 affected : 7 normal. Probably some normals were lost sight of. Another family with dominant congenital blepharophimosis in Vienna (John, 1934) numbered 10 cases (1♂ 9♀) in three generations. The sibships show 9 affected : 3 normal, but the pedigree may be incomplete. Waardenburg (1932) studied a family with eight cases in three generations which extended back through four more generations, the family having a total of 21 cases (11♂ 10♀) with one skip of a generation. Piennett (1936) describes a condition which is probably a form of ptosis. The palpebral fissure is small, very little of the white sclerotic coat is visible and the eyelids are wrinkled immediately around the iris. This dominant pedigree shows 7 cases (6♂ 1♀) in three generations.

Another dominant condition is deep brown *pigmentation of the eyelids*, several shades darker than the face. This color continues out over the entire area of the orbicularis oculi muscle, shading gradually into the surrounding parts and giving a striking appearance. I have seen this condition in a young woman with blue eyes, fair hair and fair skin color. O'Connor's (1936) family contains 9 cases (5♂ 4♀) in three generations. Peters (1918) recorded a different condition in which the lower lids only are dark owing to dilated venules and yellowish pigment beneath the skin. The condition was dominant, with 20 cases (6♂ 14♀) in five generations of a family. Bingel (1937) states that persons with fair skin and blue eyes always have light eyelids. In others they may be brown or yellow-brown to dark brown or black-brown, the color strongest in those with dark hair, eyes and skin. But dark lids can be combined with light hair and skin and nearly blue eyes. Brown lids are not seen in infants, but appear in school children. When one parent has dark and the other light lids, some children may be of each type, the brown lids being dominant. Bingel suggests that dark lids are a feature of the Baltic, Dinaric and Mediterranean races.

Treacher Collins (1900) described a classical case of congenital ***notch in the lower eyelids*** with a developmental defect of the malar bones. Berry (1888) recorded mother and daughter with a congenital notch in the lower lids and a receding chin. The mother's brother had a notch in the lid, the mother and a son having harelip. Mann and Kilner (1943) record a boy of eleven years exactly like Treacher Collins' case and a boy of fourteen months having a notch in the lower lids, both ears crumpled, no external auditory meatus and a cleft soft palate. How this sporadic abnormality is inherited is apparently unknown.

Blepharochalasis (baggy eyelids), dermatolysis palpebrarum or relaxation of the skin of the eyelids due to atrophy of the underlying connective tissue is cited by Macklin (1927a) as dominant in a French family in four generations. Panneton (1936) describes a French-Canadian girl twenty-one years old who seemed to have double congenital ptosis. Her eyes were veiled by the upper lid, giving her a sleepy appearance, but the palpebral movements were normal. The skin around her eyes had a *scrotal appearance*, being covered with innumerable little folds and more reddish than the rest, this modified skin extending to the eyebrows. The condition was scarcely evident as a young child, but developed during growth and puberty. Her nine brothers and their mother had the same defect. The mother had three sisters and seven brothers, eight of them affected. Of ninety-three affected persons in the family, in four generations, details are given of forty-seven. The sex-ratio of the affected was 43 per cent ♂ : 57 per cent ♀. The condition shows progressive expansion in the individual and a lesser degree of it is known as ***paupière en blouse.*** It appears to be not simply dominant but present in variable degree. A number of isolated cases have been recorded, born of normal parents. In another family it was recorded in mother and daughter, a third family having five cases in four generations. Carlisle in 1814 cites the case of a man with a *small pendulous fold* attached to the skin of his upper eyelid. His four children had the same peculiarity.

Distichiasis, a double row of eyelashes on each lid, is extremely rare. The extra row of cilia replaces the Meibomian glands. They are very fine and lanugo-like and may cause irritation to the eye, necessitating their removal. According to Waardenburg (1932), Wood in 1898 first found the condition hereditary, in mother and daughter. Erdmann (1904) observed it in grandmother, mother and child, and Blatt (1924) observed twenty-eight cases in four generations of one family. His eight families have a total of 114 cases (53 ♂ 61 ♀), the inheritance dominant in all, with an occasional skip. Brailey (1906) refers to four earlier cases in the literature and to four cases in the Vienna clinic of Fuchs. In one case a boy of twelve, his maternal grandfather and his mother's sister had the same malformation. This was probably an irregular dominant. The other three were single cases and may have been recessive or mutations. Fuchs observed only these four cases in twenty years with 20,000 patients annually, which would give a frequency of 1 in 100,000. Cockayne (1933) found ten families described, with twelve affected : thirteen normal in sibships, the cases being 11 ♂ 11 ♀. Thus the condition is a simple dominant. It is said to be more frequent in Russia than elsewhere, and some of the single cases appear to be mutations.

Da Pozzo (1938) finds another case, in mother and child, and Halbertsma (1935) a single case. A French family is recorded (le Double and Houssay) in which all the females and none of the males for four generations had distichiasis. This would be hologynic inheritance, with the two X-chromosomes of the females linked. The same authors record *tristichiasis* in a father and three children. Macklin (1927a) cited *lack of eyelashes* in father and son; also *fat hernia of the lids* in a mother and daughter in Germany.

Schnyder (1920) cited two families with *stenosis of the lacrymal ducts* (*dacryocystitis*). One family had six cases in three generations — an irregular dominant with one skip. Leboucq (1921) reported a sibship of six children, all affected, with normal parents. Other inherited abnormalities of the tear apparatus also occur.

Suk and Rozprým (1931) and Rozprým and Suk (1934) made a useful study of *eyebrows and eyelashes*. They described 13 forms of eyebrows and 6 of lashes in 470 Czechs. The form and color of eyebrows are independently inherited. They may be even, double, peaked, shedding, arched, etc. They may grow together or be far apart. Concurrent eyebrows are frequent in the Greeks, Cypriotes and certain other peoples. The eyelashes may be long and curved, long and straight, short and curved, short and straight, bent inward or long and hooked. A line joining the corners of the eyelid is generally horizontal in Europeans while the outer corner is generally upward in Mongolians (oblique). Routil (1933) finds the latter condition dominant over both other forms, including the occasional case of the outer angle being downward. He finds 42.2 per cent horizontal in the Ukraine and 17.2 per cent in Kizar hybrids (East Indies).

Congenital *pterygium* or epitarsus is an abnormality of the eye in which there is a fold in the conjunctiva or membrane lining the eyelid and covering the front of the eyeball. It is described as due to growth of the sclera over the cornea, which may continue until the pupil is covered, causing blindness. If removed by operation, the growth will recur. In Newman's (1913) pedigree of night-blindness it is regarded as a dominant with 9 cases (7 ♂ 2 ♀) in two generations. Armaignac (1914) described a family with 8 persons out of 22 bilaterally afflicted, not due to irritation.

For hereditary abnormalities of the extra-ocular muscles see White (1945).

Ophthalmoplegia, or paralysis of certain muscles moving the eyeball, has been traced as a congenital condition in several pedigrees in association with ptosis, each family showing a definite inherited type. The two forms, externa and interna, depend on which muscles are paralyzed. Bradburne (1912) showed dominant ophthalmoplegia externa with 16 cases (4 ♂ 12 ♀) in five generations (Fig. 54), beginning in 1710. There were no other abnormalities, but there was more or less ptosis of one or both lids accompanied by almost complete loss of movement in one or both eyes. The levator palpebrae superioris

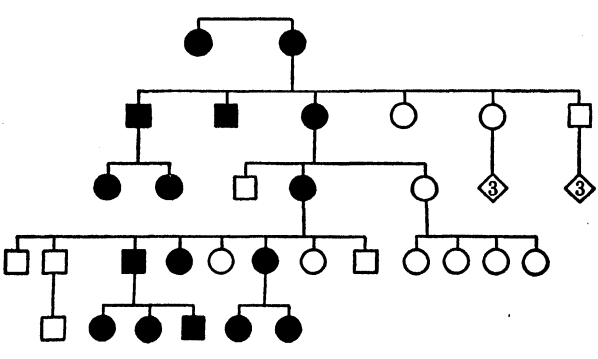

Fig. 54. Pedigree of dominant ophthalmoplegia. (After Bradburne)

muscle is said to arise as part of the rectus superior, which accounts for the association of ptosis with ophthalmoplegia. When, as here, the condition is congenital, it is one of arrested development, but many cases of ophthalmoplegia only appear in middle life. Giri (1936) describes a similar case with full references. √Recessive congenital ophthalmoplegia (Waardenburg, 1924a) appeared in five individuals (Fig. 55) of the fifth generation of a family descended by intermarriage from a common pair of ancestors. It was combined with ptosis and miosis (see below). Faulkner (1939) describes a family with ptosis and ophthalmoplegia beginning in adult life. The father and four of ten children were affected, some having double vision. The onset was at *ca.* thirty years, except in one boy in whom it began as a child. *Miosis* (extreme narrowing of the pupils) is also recessive in another family with four cases associated with ophthalmoplegia. Holth and Berner (1923) describe miosis (pinhole pupils) in three sibs. They made a full anatomical study of this extremely rare defect.

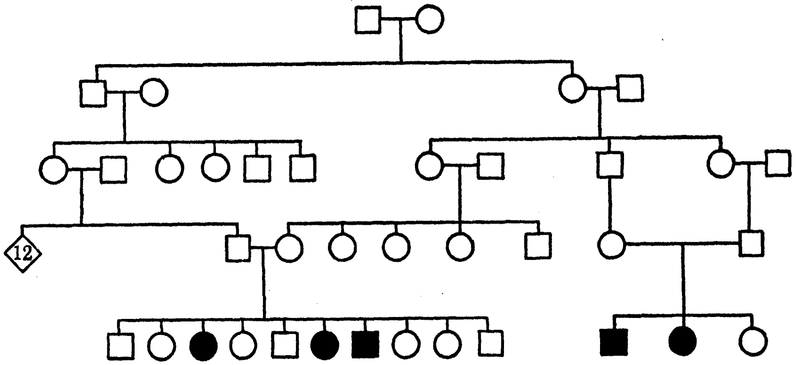

Fig. 55. Pedigree of recessive ophthalmoplegia. (After Waardenburg)

Ophthalmoplegia has been regarded as a complication of exophthalmic goitre (*q.v.*) or as evidence of the association of exophthalmic goitre with myasthenia gravis (paralysis of particular muscles without atrophy). Brain (1938) studied thirty-one cases and concluded that exophthalmic ophthalmoplegia is a syndrome distinct from either. It differs from exophthalmic goitre in age and sex incidence and in the role of the thyroid in its etiology. In Graves' disease, thyrotoxicosis is the principal disorder of function; in exophthalmic ophthalmoplegia it plays no essential part. The exophthalmos (protruding eyes) is attributed to a factor other than thyroxin (Chap. XIII), and ophthalmoplegia to a mechanical effect of intra-orbital tension on the ocular muscles. The thyrotropic hormone of the pituitary probably plays a part.

Lagophthalmus is the opposite of ptosis; the retraction of the upper lid is accentuated and there is inability to close the eyes. This may be caused by various conditions and is non-hereditary. It frequently occurs in connection with leprosy. Peters (1915) described a family with five cases of congenital lagophthalmus in four generations. It is dominant and the fact that the five affected were all females may be only chance. In *cryptophthalmos* or ablepharia the lids, which normally separate in the seventh month, fail to do so. The cornea and eyeball may also be abnormal. The condition is often unilateral. In the literature thirty-seven cases have been described, the inheritance evidently recessive as a rule, but in two cases mother and two children were affected. It has also been seen in three generations (eight cases) of mice. Brodsky and Waddy (1940) describe an infant with bilateral absence of palpebral fissures, eyelashes and eyebrows. The nasal bridge was wide and flat, the fingers and the three middle toes webbed, the external genitals malformed. Coover (1910) described a less extreme case of bilateral cryptophthalmia in mother and child, with no other abnormality.

Partial union of the eyelids, *ankyloblepharon*, was found by Goldberg in five members of a family in four generations, the inheritance dominant and the defect generally on the outer side of the eye-opening. Normally the epidermis of the lids remains fused only until the seventh month. Ford (1925) described father and son with congenital ankyloblepharon. In the father the levator palpebrae superioris muscle was absent. Fine (1933) found two affected brothers. In both eyes a web of skin covered the caruncle and there was a suggestion of a similar condition in the mother.

Entropion or inversion of the eyelids sometimes looks like the Mongolian fold except that the epicanthus remains exposed. Usher (1932) described spasmodic entropion in five generations of a fisherman family in Aberdeen, invariably in the lower lids. There were 9 cases (8♂ 1♀), as well as 4 of entropion with changes in the skin of the eyelids and 17 of changes in the skin of the lids only. These changes were of three kinds, (1) swelling of the upper lids, (2) a fold like the Mongolian fold, (3) crinkling of the skin of both lids. The inheritance is dominant and the entropion is believed to be secondary to the skin changes.

Müller (1931) described a family with congenital entropion resulting from epiblepharon (eyelashes pressing against the eyeball). The grandfather, mother and two children were affected, and in another family a brother and sister as well as three sons of the brother. The condition appears to be dominant and is probably not very rare. Forty cases were found in the literature.

Strabismus or Squint

Strabismus, or squinting, is often due to defective musculature of the eye, and is stated by Sedgwick (1861) to be hereditary in some families for many generations. In one family the five boys squinted in the left eye or in both eyes, while the five girls were normal. Their father and mother were normal, but the mother's sister had a boy and a girl both squinting with the left eye.

Czellitzer (1928) studied the inheritance of squinting in 306 families with 365 squinting children in Berlin. Cohn found among 10,060 school children, 2.2 per cent of squinters. Among their sibs numbering 891, Czellitzer found 140 cases, 15.4 per cent. Inward and outward squinting are distinguished. He concludes that the condition is recessive, but not due to a single factor, and he finds it more frequent in women (54.5 per cent). Macklin (1927) cites pedigrees in which it is recessive, and another in which it is dominant, while Clausen (1923) thinks that in still others it is due to the presence of several factors. Man appears to be one of few species in which the same character may behave as a dominant in one pedigree and a recessive in another. This condition can now be recognized as fairly common in the human species, and it requires a special explanation. It is known that in certain genera of plants "doubling" of the flowers is a dominant, while in others it is recessive to normal, but so far as known there is constancy in the type of inheritance in any one genus or species. Morphologically, doubling involves different changes and the doubling is not the same in all cases. The explanation may be that in man millions of individuals are under observation, but this seems insufficient. Such cases have been known in Drosophila, but their possible significance has not been considered.

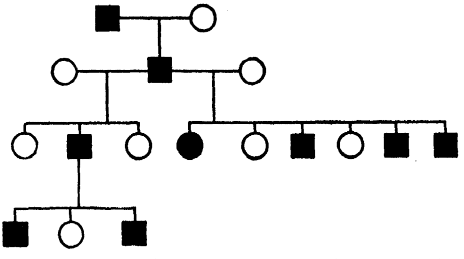

Fig. 56. Dominant pedigree of hyperopia, amblyopia and strabismus in the left eye only. (After Sicherer)

Hippocrates observed that a parent with a cross-eye often had a cross-eyed child. Both convergent and divergent squint are inherited. The convergent form occurs 15 times (8♂ 7♀) in 4 generations in a pedigree of Clausen and Bauer, indicating dominant inheritance. Worth (1906) examined 1373 cases in London and found squint in parent, grandparent, brother or sister in 51 per cent of cases. The development of squint is also associated with nervous and psychological factors. Sicherer (1907) gives a dominant pedigree (Fig. 56) of strabismus, hyperopia (long-sightedness) and amblyopia (dimness of vision) in the left eye only, with 8♂ and 1♀ affected in four generations. The right eye was emmetropic (normal) except in one case in which it was hyperopic. This appears to be a single mutation affecting several features of the eye. There are many other records in which one gene appears to affect two or three parts or functions of the eye. Strabismus and nystagmus are both frequently associated with other defects.

Rodin (1926) reported a family in which the mother and the three youngest children in a family of fourteen (nine living) squinted, with no ancestral history of the condition. In such a case the condition might be recessive or a dominant with low penetrance. He subsequently (1934) found another family of seven children in which the three youngest squinted although the parents were normal. Why the youngest children only should tend to develop the condition is not clear. West (1939) cites a family in which strabismus and nystagmus are both present. He summarizes the previous records, showing that both these conditions can be inherited as dominant, recessive or sex-linked, the first two types of inheritance being nearly equally frequent and the last rare.

Strabismus takes a number of forms, such as unilateral, alternating (bilateral, one eye at a time being in use), concomitant, convergent, divergent, vertical, intermittent, paralytic and spastic, the last two being due to muscular abnormalities. When strabismus and nystagmus occur together, as they not infrequently do, it is still a question whether they are produced by one gene or two. It appears probable that strabismus itself is a one-gene condition and that the conclusions of Clausen and Czellitzer, based on statistical studies, that two or more genes are required, is due to the rather low penetrance. Non-inherited strabismus of slight degree can arise through worry. Inman (1935) shows that there are well-authenticated cases in which emotion causes periodic disease of the eye, including glaucoma, ocular hemorrhage, iridocyclitis, conjunctivitis, styes and tarsal cysts.

Regan, Gregory and Mead (1944) find that strabismus is a simple recessive in a herd of cattle in California. It develops to various degrees during the first year and in some cases the eyes also protrude.

Nystagmus (a continuous rhythmic rolling movement of the eyeballs) is associated with many congenital defects of the eye and is frequently accompanied by shaking of the head. It may be lateral, vertical, rotary or mixed. Miners' nystagmus is a well-known occupational neurosis. Waardenburg (1935) concludes that the nystagmus connected with albinism and other ocular defects is the result of a defective macula lutea or a lack of innervation of the eye. Hemmes (1926) found astigmatism present in 64 per cent of cases of nystagmus. He suggested that if the tone of the muscles controlling the eyeballs is not weakened equally in all, nystagmus would arise. He also suggested a connection with the equilibrium apparatus of the ear, but no satisfactory explanation has been reached. Nettleship gives a sex-linked pedigree. Holm (1926) points out that in certain pedigrees it is a simple dominant, while in others it is confined to the sons but transmitted by the daughters. At least eleven pedigrees of the latter type have been published, and some others partly follow this recessive sex-linked type. The dominant and the sex-linked type are alike in their symptoms: shaking of the head, astigmatism, and weak eye pigmentation (partial albinism). It should be considered as due to a defect in the development of the eye, causing amblyopia (dim sight). Holm gives two pedigrees, both sex-linked. One (Fig. 57) has ten cases in four generations, the other, seven cases in three generations. As a dominant it is generally (like strabismus) irregular, i.e., of reduced penetrance. The simple recessive form is less well established than the dominant and sex-linked. Waardenburg (1935) finds that the eye is often albinotic and thinks Vogt's cases of sex-linked fundal albinism are the same thing as nystagmus.

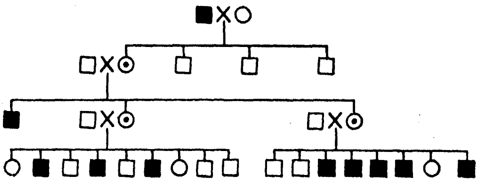

Fig. 57. Recessive sex-linked pedigree of nystagmus. (After Holm)

Allen (1942) records a family with primary nystagmus and neither defective macula nor albinism. It was strictly dominant, with 11 cases (5♂ 6♀) in four generations, sibships 10 affected : 7 normal. The lesion is regarded as having its origin in the central nervous system, as in members with more stable nervous systems the defect was less noticeable. Billings (1942) records another family with recessive sex-linked nystagmus, nine cases, all males, in four generations. DeKleyn (1938) shows that intoxication of the rabbit produces a vestibular nystagmus. This condition can also be elicited after removal of most of the brain, leaving only a reflex arc from the labyrinth to the external rectus muscle. In an anencephalous human monster which survived at Utrecht for a week, on stimulating the vestibular organs a nystagmus with slow and quick phase was elicited in both directions.

Hemmes (1924) analyzed his 38 pedigrees into sex-linked pedigrees, 96 **♂**: 40♂ : 1 **♀** : 89 ♀, and "mixed" (autosomal) 130 **♂** : 127♂ : 100 **♀** : 165 ♀. Waardenburg (1935) finds the general sex-ratio in all sibships of sex-linked nystagmus to be 150 **♂** : 127 **♀**, and including the dominant cases, 261 ♂ : 209 ♀, the same relations holding for other sex-linked ocular abnormalities. There is also a large excess of affected to normal (66.2% ± 2.93). He formulates the general rule that *the mutation-causes which produce recessive and irregular dominant sex-linked eye characters in man also cause a higher ratio of male births and at the same time an excess of affected boys.* Probably also the number of heterozygous females (carriers) is significantly higher than that of normals. If this law is generally applicable to ocular conditions it is probably of still wider application in human inheritance.

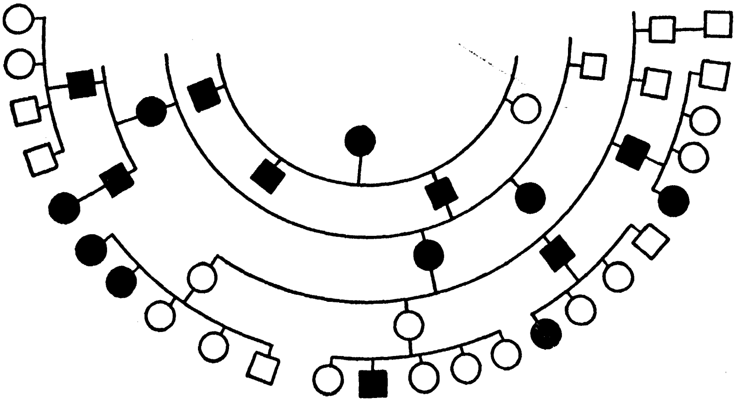

Fig. 58. Irregular dominant sex-linked pedigree of hereditary nystagmus. (After Hemmes)

Lenz (1932) holds that there are several allelic genes, each producing a different form of nystagmus. Hemmes (1924) found the frequency of nystagmus in Holland to be 1 in 5000 for ♂ ♂ and 1 in 10,000 for ♀ ♀. One of his pedigrees has 14 affected males in four generations, strictly recessive sex-linked, but with only 8 normal brothers. Of the daughters, 6 are transmitters and 5 (all with families) not. In 12 of Hemmes' 38 pedigrees there are affected females. Eight of these, with no skip, pass for regular dominant sex-linked. Figure 58 shows a pedigree of Dubois, copied by Lenz from Hemmes, in which the inheritance is irregularly dominant sex-linked, 8 ♂ : 9 ♀ affected. In IV. 3 and IV. 4 there is failure of penetrance. The causes of reduced penetrance and irregular dominance remain uncertain. The subject is discussed on p. 15.

Steggerda (1928) described a family with mixed nystagmus, 13 cases (6 ♂ 7 ♀) in three generations. The gene was apparently a simple dominant, three other members of the family having "weak eyes." Weissenberg's (1928) Jewish family in the Ukraine (Fig. 59) has nystagmus alone, although the sight is necessarily not sharp. If dominant, the condition has low penetrance, since the 10 children of II. 2 were all normal.

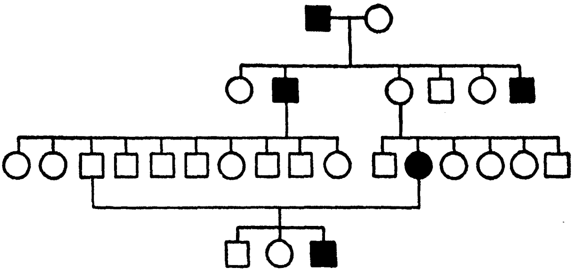

Fig. 59. Irregular dominant pedigree of nystagmus in a Jewish family in the Ukraine. (After Weissenberg)

Waardenburg (1938) has published an instructive case of identical twins who were discordant, in a pedigree of irregularly dominant sex-linked nystagmus. The twin who failed to develop the condition nevertheless transmitted it to children. This shows that *penetrance may fail even when the genetic background and the prenatal environment are the same.* It remains a question whether the latent nystagmus associated with albinoid conditions is genetically distinct. It is more probably a result of the albinism. Kitihara (1930) described five families in Japan with nystagmus and found eighty in the literature. When sex-linked it can be transmitted by males and shows variable dominance in the female. The extensive case of Hemmes (1924) is of special interest (Fig. 10, p. 22) because he considered the condition dominant in the descendants of I. 1 but recessive sex-linked in those of I. 3. This implies the translocation of the gene in certain germ cells of the mother of these brothers, from an autosome to the X. Levit (1936) takes exception to this view and believes that the descendants of I. 3 show a more conditioned autosomal dominance. He cites V. 31 as a heterozygous female showing the trait, but with this exception it must be admitted that the results fit perfectly the theory of a sex-linked recessive and it is strange, on his view, that none of the seven females in this part of the pedigree show the condition although they have all transmitted it. Hemmes' view is the more probable.

The essential parts of the eye are shown in Fig. 60. Not only the eyelids and the muscles moving the eyeball but every other part of the eye is subject to inherited defects. As the eye is the most precise and delicate organ in the body, these defects have all been intensively studied and only a fraction of the recent investigations can be referred to here.

Steiger showed that the *cornea* of the eye in 1500 children varies from 39 to 48 diopters in refractive index, the whole series falling into a binomial curve, with mode between 44 and 45 diopters. Gasser (1938) measured the condition in 220 eyes belonging to four different family groups. Two families gave curves with mode at *ca.* 43.5 diopters, another gave a very high peak at 45–46 with one value (segregation) as high as 52.5, and the fourth at 44–45. There were indications of both dominant and intermediate inheritance of *corneal refraction*, with probable recessiveness in one case, in which extremely high corneal refraction was combined with an excessively short ocular axis.

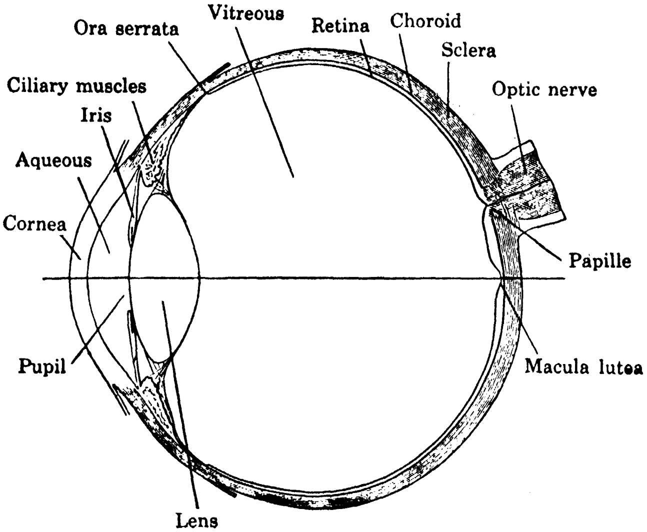

Fig. 60. Essential parts of the eye. (From Waardenburg after Merkel)

Gasser also confirms Steiger in the conclusion that weak refraction is combined with large interpupillary distance and strongly curved cornea with small interpupillary distance. The interocular distance has been connected by some authors with size of brain. From portraits of the seventeenth and eighteenth centuries one gets the impression that interocular distances were formerly greater than now.

In *astigmatism* the radius of curvature of one plane of the cornea or the lens is longer or shorter than in the plane at right angles. Astigmatism was unknown until the beginning of the nineteenth century and cylindrical glasses were not made until 1820. According to Macklin (1927d) the axis and degree of astigmatism are generally the same in all affected members of a family. However, Waardenburg finds considerable variation within families and in identical twins, so he regards astigmatism as a condition showing considerable lability and frequently intermediate inheritance. A person may also have unilateral astigmatism and his child bilateral, or vice versa. Waardenburg (1932) gives a pedigree of recessive astigmatism in which two astigmatic parents had eight children, all affected, the father's sister being astigmatic but with three normal children. In some other families the condition is an irregular dominant. Motolese and Berardi (1936) made a study of corneal astigmatism in about fifty families of parents and children. Either parent could transmit. Probably corneal and lenticular astigmatism are genically independent, so the presence of both in one family or individual may lead to confusing results.

Wieser (1927) tested the eyes of forty-six Sudan Negroes (Senegalese and Foula) from Dakar in a touring troupe at Zürich. The sharpness of vision of 85.5 per cent was over 1; 23.3 per cent were over 2.4. By comparison, among 10,000 Swiss recruits 73.4 per cent were over 1. The Sudanese could all see better by natural than by artificial light. Most of them were hyperopic, some emmetropic, none myopic and none showed corneal astigmatism. These results confirm other observations on the eyes of uncivilized peoples.

In *keratoconus* the cornea is bulged outward in the form of a cone by internal pressure. It is recessive in some pedigrees but more frequently an irregular dominant. Van der Hoeve's family is in the latter class. Sander (1931) described a Maltese family, father and three daughters all with keratoconus and anterior polar cataract in each eye, with myopia, mental degeneration and anaemia. Vogt (1934) found two cases of keratoconus in cousins (female) descended in the second and third generation from a pair of ancestors. The condition must either be recessive or a dominant of very low penetrance. A case of enlarged cornea (bilateral) combined with arachnodactyly is recorded (Stephenson, 1945) in a baby girl. There were no crypts in the iris, there was slight polydactyly and wasting of the arm and leg muscles. Five sibs were normal, the parents were unrelated, the grandparents likewise normal.

Hereditary *corneal dystrophy* is known in several forms: nodular (granular is a better term), cloudy, crystalline, lattice-like and mixed forms, according to the type of degeneration. Bücklers (1939) classified them as mainly of three types: (1) dominant granular or crumb-like, (2) recessive macular type, (3) dominant lattice type. These opaque non-inflammatory spots may appear at puberty, but in some families they are congenital; they progress slowly but may end in blindness. They may be regarded as corneal cataracts. Myopia is also generally present. The condition was described by Groenouw in 1890. It is bilateral but relatively rare. McBain (1942) reported two cases of the early granular type. Franceschetti and Babel (1944) have a further classification of hereditary types of corneal dystrophy, based upon that of Bücklers.

Folkar (1909) traced *nodular opacity of the cornea* through three generations, finding nine cases. Opacity of the corneal margin, known as *arcus juvenilis* or embryotoxon, was inherited in Clausen's pedigree in four generations as a dominant, occurring in twenty-one out of thirty-two members. The inheritance of corneal cataract is generally dominant. Greenwood's (1931) family included five cases of bilateral progressive lattice dystrophy in three generations. Those affected were all overweight. Srinivasan (1931) described a peculiar case in Madras (Fig. 61) with seven females affected in two generations. The original parents were normal. Their three daughters showed the lattice-form. Of the grandchildren, III. 1, 2 had the nodular form, while the two youngest showed the beginning of dystrophy with keratitis punctata and curdy spots mostly on the corneal nerves. Groenouw's (1933) family with the nodular form has eight affected members (1 ♂ 7 ♀) in four generations, the sibships numbering 7 affected : 12 unaffected. The original great-grandfather married twice and transmitted the condition through both wives. Riegel (1933) described five cases (1 ♂ 4 ♀) in a family in three generations. The degeneration was bilateral and in the third generation was almost congenital. A pedigree of corneal erosion and degeneration combined (except in one man who showed only corneal degeneration) included 12 cases (5 ♂ 7 ♀) in three generations (Schappert, 1933), the sibships 12 affected: 20 normal. Judd's family (1933) includes 9 cases (2 ♂ 7 ♀) in three generations. They were all very tall and slender, suggesting pituitary dysfunction. Frykholm's (1935) pedigree with 18 cases (7 ♂ 11 ♀) in six generations is strictly dominant, with no skip. There is, as usual, an excess of affected females. In this pedigree the lattice form occurs mainly in the young and a more nodular form in the older. Freiberger and Josephson's (1936) family contained 13 cases (6 ♂ 7 ♀) and polarized light revealed the presence of cholesterol in the opacities. Tritscheller's (1921) dominant pedigree of crystalline corneal dystrophy, with 16 cases (9 ♂ 7 ♀) in three generations, is remarkable for the fact that the ancestry was found to converge on a single pair four generations earlier. This indicates (owing to the relationships) that the condition had been transmitted as a recessive (or dominant without penetrance) for four to six generations before appearing as

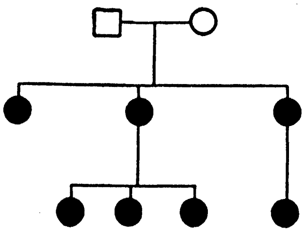

Fig. 61. Pedigree of Groenouw's nodular dystrophy of the cornea. (After Srinivasan)

a dominant in two families of the fourth and two others of the fifth generation. Richner (1938) described a case of corneal affection combined with keratoma palmare et plantare (*q.v.*) in a boy of seven years with normal parents. The cloudiness of the cornea was in spiral form. There are only four previous records of this rare combination, which appears to be recessive.

Gilch (1937) made a study of corneal turbidity in Wurtemburg, finding 68 cases, with which he combined 51 from the literature. All but 5 of the 119 cases fell into 12 pedigrees, each having a definite type of corneal cataract. Three general types are recognized: (1) brittle or crumb-like corneal dystrophy, which is dominant, (2) macular or spotted, which is severe and recessive, and (3) the lattice or reticular form, which is dominant but rare. The last two types both lead to blindness, but the brittle type is less severe. Corneal cataract is characterized by being bilateral, beginning in the first decade and slowly but steadily progressing. The brittle form nearly doubles in each generation, but the men are still able to see and work at fifty or sixty. The recessive form appears in the third decade and they often have less than one-tenth normal sight. Many of the cataracts are good examples of homochronous heredity, the condition appearing at roughly the same age in successive generations. As there is no method of preventing near-blindness from this condition, reproduction should be prevented in families in which corneal cataract occurs. See the monograph by Bücklers (1938). Schutz (1943) describes a family with eleven cases of the dominant crumb-like form, bilateral, but the sight only slightly affected.

Mutch (1944) states that in dominant forms the axial zone only is affected and there is no vascularization. His family has 24 cases (14♂ 10♀) in four generations, dominant. He gives a full review of the literature and suggests that persons with this defect should be sterilized. Dominant pedigrees are more numerous than recessive. Mutch had fifty-two members of his family tested for the ABO and MN blood groups, finding no linkage. But many in the family had blue eyes and no affected member had brown eyes, so there is possible linkage with a gene for eye color. He also classifies the types of corneal dystrophy as granular and reticular (both dominant) and macular (recessive). Attenborough (1945) records three sisters with dominant granular corneal dystrophy. Their father, grandmother and great-grandfather were also affected.

Theodore (1944) describes six cases of congenital opacity of the cornea, including two sisters. Three of them also had microphthalmia.

In a family of Sala (1932) the males in three generations have a peculiar opacity of the cornea combined with aniridia and opacity of the lens. Doggart (1939) describes a family with *keratitis* (inflammation of the cornea) in a man, his daughter, his mother and his mother's father, indicating dominant inheritance. This condition is also induced in such occupations as artificial silk manufacture and the opening of oyster shells.

Epithelial dystrophy of the cornea is very rare. The original account is by Fuchs in 1910. He described it in 13 elderly persons (9) ♀ with failure of vision in one or both eyes. Doggart (1931) describes the only familial case, in two sisters. Descemet's layer, adjacent to the inner endothelial layer, is first affected. Davenport (1927a) recorded a family with five females in three generations affected by *choroid sarcoma*, inheritance probably dominant.

Thomson and Ballantyne (1903) described a case of *pigmentation of the cornea* in which there was a faint brown vertical line composed of chocolate-colored dots in the middle of each cornea, combined with myopia and partial coloboma of each disc. Five previous cases exactly similar (four of them with myopia) suggest a genic basis for this condition. In *cornea plana* the curvature of the cornea is the same as that of the sclera. Cockburn (1944) finds it in a Greek soldier, and it appears to be recessive (Duke-Elder, 1940).

Anophthalmos (absence of eyeballs) is an extremely rare condition. Lycosthenes in 1557 relates of a child born without eyes or ears but otherwise normal, and Thomas Bartholin in 1657 gave the earliest creditable account of lack of both eyes in a child with maldevelopment of nose and mouth and with six fingers and toes. Monteath in 1821 recorded a family in Glasgow in which the first, second and fourth of eight children were born with no eyeball. Walker observed in Manchester in 1832 two children (sisters) with congenital anophthalmos. A normal boy was born between them. Sorsby (1934) published a manuscript in the Library of the Royal College of Surgeons, by James Briggs, giving the earliest account of familial anophthalmos. Both parents had rather small eyeballs and four of the seven children were blind with no eyeballs. In II. 7 the right eye was absent, the left malformed. The father had two normal children by a second marriage. These records go to show that the gene for anophthalmia is recessive, the eyeball being small in heterozygotes. Eyelessness may be accompanied by syndactyly and hydrocephalus and the optic nerves may also be affected. Waardenburg (1935) cites a family with three cases of eyelessness, syndactyly and only four toes on each foot.

King (1931) estimated that anophthalmos occurs in rats not oftener than 1 in 1000. Eyeless rats are usually smaller and less vigorous. From breeding such rats to normals and backcrossing, only normals were obtained, from which she concludes that anophthalmos is not inherited. It seems, however, that the tendency to produce anophthalmic offspring is inherited both in rats and man. This probably means that a definite gene for anophthalmia is present, its expression depending on the conditions at a critical stage in eye development.

In pigs, it has been shown (Hale, 1933) that a sow receiving a ration deficient in vitamin A gave birth to a litter of eleven pigs, all without eyeballs, although ten were alive. In another case (Zilva *et al.*, 1921), lack of vitamin A produced a litter of eight in which two pigs lacked hind limbs and in two others the hind legs were abnormally developed. Possibly the different response to lack of vitamin A depended on genetic differences in the pigs. Eaton (1937) described a strain of guinea pigs in which anophthalmia on one or both sides, microphthalmia, opaque lens and rotated eyeball were all genetically related but the method of inheritance was uncertain. The condition was sublethal.

Abnormally *long lower tear duct* with ankyloblepharon internum and a large caruncle was described by van der Hoeve in 1915 in a father and four children. Waardenburg (1930) cites several other families in Holland, the grandmother in one family being affected. The condition thus appears to be dominant. He also cites a family with ptosis, blepharophimosis, hypoplasia carunculi et plicae semilunaris, epicanthus, hyperplasia regionis interocularis with dislocatio lateroversa canthi medialis et punctorum lacrimalium. These conditions were all inherited as a simple dominant unit — a case of foetal fixation. Town (1943) describes the *absence of lacrimal puncta* in a father and his two boys. Tears always ran down the boys' cheeks. He found 21 cases of this rare condition — absence of puncta and canaliculi — on record, in one of which it was present in the grandfather.

Microphthalmus

Microphthalmus is a condition in which the eyeball is so small that vision is subnormal or absent. The defect occurs in varying degrees, with anophthalmus as its extreme form. In true microphthalmia the small eyeball is accompanied by a small palpebral fissure and orbit, whereas in *microcornea* only the eyeball, or strictly the anterior (corneal) part of it, is small. The inheritance of microcornea is rare and requires further investigation. It appears to be recessive in certain cases and perhaps polymeric (multifactorial) in others. Sometimes the children of microphthalmic parents show high-grade farsightedness, which is probably the heterozygous condition. Macklin (1927b) records seven pedigrees in which microphthalmia is a recessive, born of normal parents. Usher (1921) described a case where it is dominant, associated with myopia and corectopia (displacement of the pupil) in four generations. In a pedigree of Ash (1922) it is of the sex-linked type (Fig. 62). Ash makes the statement that "the male members show no tendency to transmit the disease." This is because none of the affected (blind) males married. Had any of them done so, their daughters would no doubt have been transmitters of blindness to half the males of the next generation. Chr. Thomsen (1915) reviews the early literature and describes families having microphthalmia with or without cataract. Microphthalmus is thus a further example of the fact that the same condition may be inherited as a Mendelian dominant or recessive, or as a sex-linked character, in different lines of descent.

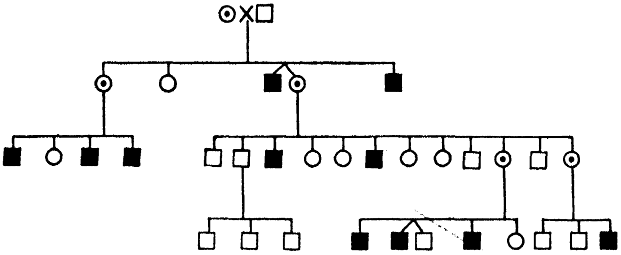

Fig. 62. Recessive sex-linked inheritance of microphthalmia. (After Ash)

Wolff (1930) records a family in which the parents were first cousins and 5 of the 10 living children (2♂ 3♀) had small eyes, deeply set, with small orbits. There was some ptosis but reasonably good vision, and all were highly hypermetropic. The cornea was *ca.* 10 mm. in transverse diameter. As shown in Fig. 63, three of this family (III. 4, 7, 10) had only two upper incisors, III. 4 had four abnormally small lower incisors and III. 8 had supernumerary teeth (two rows). Darwin,

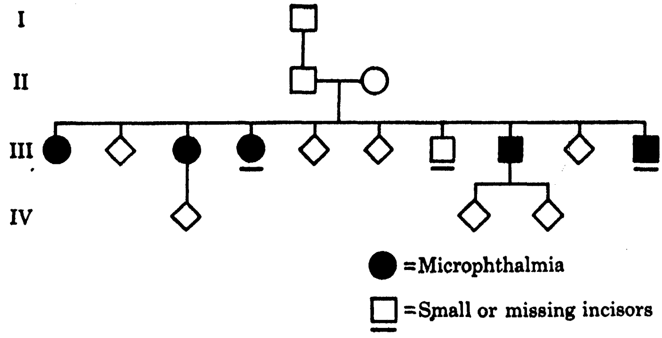

Fig. 63. Pedigree of small eyes and small or absent incisors. (After Wolff)

in *Animals and Plants under Domestication*, recorded this association of microphthalmia with defective dentition and other cases have been recorded since. Brailey (1890) recorded the case of a girl of eighteen with double microphthalmus, the irides nearly absent. In her upper jaw only the canines and two premolars on each side were present; in the lower jaw the incisors were wanting on the right side and the canine on the left. She was the eldest of six children and had atresia ani and umbilical hernia at birth. Three sisters suffered from convulsions and two were normal.

The sex-linked recessive pedigree of Ash (Fig. 62) has since been extended by Fraser Roberts (1937), who shows that the microphthalmia in this family is associated with mental defect. There are now fifteen cases in five generations. The microphthalmia shows much variation and blind males may range from normal mentality to feeblemindedness and idiocy. There is no mental deficiency apart from blindness in the family. The normal members are above average intelligence. This association of microphthalmia with mental impairment has been noted by several writers. Roberts explains the association by suggesting that the organism at certain critical stages of development is, for genetic reasons, abnormally sensitive to non-genetic influences which can modify the brain. Microphthalmia is also a dominant in association with ectopia lentis and myopia (pedigree of Usher) as well as with other ocular defects. The Ash family was traced back by Iles (1939) for two hundred years in Yorkshire, from members at Stoke Park Colony. Affected members are all born blind, and no two eyes are alike. The family is now nearly extinct.

Page (1874) described three generations of microphthalmos, irideremia and nystagmus, occurring in a woman, two daughters (two sons and a daughter unaffected) and an affected daughter's daughter.

In Helen King's (1931) strain of albino rats an individual female appeared with a small right eye. The other twenty-eight offspring from this pair of parents were all normal, nor did sibs yield any further case. Mated to a brother, this female gave nineteen young, including one female like the mother. The latter was mated to a brother and produced 19 young, including 4 which were microphthalmic: 1 ♂ 1 ♀ with small left eye, 1 ♀ with small right eye and 1 ♂ with both eyes small. From this strain 1884 rats were bred, 538 of which had one or both eyes defective, but it was impossible to obtain a strain pure for microphthalmia, which shows that the *tendency* rather than the condition was inherited. In a study of 14 further generations from this stock, Hain (1936) bred over 5000 rats but obtained only 154 with eye defects, including besides microphthalmia, aniridia, cataract, etc., and rarely anophthalmos. Defectives were rarely born to defective parents. The genic situation appears to be too indefinite and too subject to environmental conditions to bear analysis. Hain suggests that a dominant factor with poor expressivity is present, conditioned by genetic modifiers and physiological effects.

Szily (1924) made an extensive histological study of microphthalmus, coloboma and orbital cysts in rabbits' eyes; also in pigs and other animals. By treatment with naphthalene he produced coloboma fifty-five times as frequently as through normal inheritance. In fowls, bilateral microphthalmia in which the eyeball was about half the normal diameter was inherited (Jeffrey, 1941) as a simple recessive (196 : 60). The comb was also partially or completely doubled, and the condition was lethal as the chicks could not see to eat or drink. Gruenwald (1944) shows that the abnormal development begins with the formation of minute cysts in the retina, which is later thrown into folds. The lens is only slightly reduced in size, but the pecten is almost absent.

In *megalocornea* the eyeball is abnormally large. This may result from glaucoma (hydrophthalmus) in childhood, but is usually an independent abnormality accompanied by very good sight. It cannot therefore be regarded as a defect. Kayser (1914a) gives a family pedigree with sixteen cases in five generations. It was found only in males, and except in one case it was not inherited direct from father to son,[3] but through normal daughters of affected fathers, hence ordinary recessive-sex-linked. Kayser (1914b) described another family with seventeen cases in six generations, the inheritance being through sound mothers to half their sons. Grönholm (1921) gives another pedigree with the same type of inheritance, 12 ♂ 2 ♀ affected in three generations. This includes a marriage between a woman transmitter and a man with megalocornea. They have two daughters affected and one normal son. This is in accordance with expectation for $\underline{X}X \times \underline{X}Y$. Finally, Gredig (1926) describes a family in which the condition is inherited as an ordinary Mendelian dominant, with 13 occurrences (11 ♂ 2 ♀) in four generations. He, like earlier authors, points out the difficulty in distinguishing megalocornea from hydrophthalmus or dropsy of the eye.

Waardenburg (1932) thinks that Gredig has not proven simple dominance of megalocornea in this family. He finds evidence that in some families a graded series of size factors with cumulative effects is involved, this condition being distinguished as *macrocornea*. He suggests that in Gredig's pedigree both conditions are present. A family with recessive sex-linked *megalophthalmus* is described by Vail (1931). The condition was bilateral, almost confined to males, and it leads to cataract.

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[3] This son was born in 1810. His son and four daughters were normal, and three of the daughters had 10 normal children (5 ♂ 5 ♀), so there may be a mistake in the record of this man.

Julia Bell (1932) gives ten pedigrees of megalocornea with 53 ♂ 6 ♀ affected, indicating that it is generally recessive sex-linked. Riddell (1941) states that it is frequently difficult to decide whether the cornea is too large for the sclera or the eyeball too small for the cornea. His pedigree is sex-linked, with four males and one heterozygous female affected in three generations, showing that dominance is variable in the female. The mean diameter of the cornea was 12.625 mm. in affected members, 11.542 mm. in unaffected, controls ranging from 11–12.5 mm. The presence of this sex-linked gene may account for the fact that the mean diameter of the cornea is larger in males than females.

Hydrophthalmos (distention of the eyeball by an internal accumulation of water) resembles megalophthalmos clinically but differs in causation. Vogt crossed hydrophthalmic rabbits with normal and found it inherited as a recessive.

Melanosis sclerae is a rare condition in which a large amount of brown melanin pigment accumulates not only in the iris but also in the sclera, which may be bluish in places. Jablonski described two sisters with both eyes affected, but frequently only one eye undergoes the change. Selter reported four cases in two generations.

The *pupillar membrane* over the iris, which is normally resorbed in the eighth month, sometimes persists in the form of a network or free clumps of pigment. This happens more frequently in dark brown than in blue eyes. Such conditions have been seen in grandmother, mother and daughter of one family, as well as in brother and sister and in three sibs, together with other conditions.

Ectopia lentis, or dislocation or displacement of the lens, is a condition which occurs in various degrees and interferes more or less with vision. Vogt (1905) described a family in eighteen members of which spontaneous dislocation of the lens took place during middle age (at twenty to sixty-five years) and was inherited as a dominant. Fifteen out of thirty males (50 per cent), but only three out of twenty-six females (12 per cent), showed the condition, and the latter did not transmit. Waardenburg (1924b), in a study of these conditions, distinguishes ectopia pupillae, ectopia lentis congenita, ectopia lentis et pupillae and ectopia combined with other abnormalities. Usually ectopia of the pupil is unilateral and uninherited. Waardenburg gives a dominant pedigree showing 15 persons (6 ♂ 9 ♀) in four generations with bilateral ectopia. The inheritance is usually dominant in other pedigrees. The direction of the displacement is always upward and inward, but it occurs in grades from scarcely abnormal to the largest displacement. Usually also the pupil is narrow, there are structural changes in the iris, remains of the membrana pupillaris and absence of the limbus. The condition is independent of iris color. Ectopia lentis is also found to be recessive in three other families.

Cameron (1926) described hereditary dislocation of the lens in four generations (Fig. 64). Fourteen persons are affected, only one a male. Both lenses were dislocated in every case, the vision was seriously affected, and a squint (convergent or divergent) was apparent. Five members had to be trained in an institution for the blind. The condition was female-sex-linked with the one exception, but seven females were unaffected, so it is not a case of united X-chromosomes, unless they separated in the mother of the affected male. Fecht (1926) describes luxation of the lens in three brothers and a sister. The parents were normal, as were the next generation from marriages with normals. Evidently the condition was recessive in this pedigree.

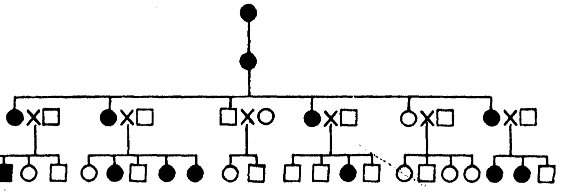

Fig. 64. Pedigree of ectopia lentis. (After Cameron)

In Windle's (1891) family with congenital ectopia lentis the condition was strictly dominant, 13 cases (11 ♂ 2 ♀) in five generations, sibships numbering 12 affected : 15 normal. Usher (1924) described a family with seven cases in three generations, both lenses dislocated in every case. An affected father had five affected and four normal children, one of the former having an affected son. As the father's parents were normal and the condition is strictly dominant, it probably arose as a mutation in this family, especially as the father alone was affected among nine sibs. Kredbova's (1932) family shows dominant inheritance in four generations, 15 of 37 persons being affected. Two of them had also coloboma of iris and choroid and six had fundus changes with a high degree of myopia. Roese (1933) described four generations of a family with 9 cases (5 ♂ 4 ♀) and strictly dominant inheritance. Pittenger (1935) has another pedigree with 22 cases (10 ♂ 12 ♀) in five generations, but it is so constructed as to be almost unintelligible. The family was of good mentality and there was no consanguinity. Myopia was the rule, but the vision of only two patients was improved by glasses. Falls and Cotterman (1943) describe a family with 24 cases in six generations, dominant but with failure of penetrance in two cases. Cataract frequently developed later. Cotterman and Falls

(1944) have tabulated material from 157 members of this family for an analysis of linkage with the ABO blood groups, MN blood types, Rh, secretor factor, taste-blindness, eye-color and red-green color-blindness (9 cases). Measurements showed no evidence of arachnodactyly.

Ectopia lentis combined with arachnodactyly and blue sclera with brittle bones are considered in Chap. XVIII.

Adie's syndrome is a condition in which the pupils are unequal (Fig. 65); they react slowly on accommodation but not to light, and tendon reflexes are absent. It was pointed out that the condition is harmless (Adie, 1931) although the Argyll-Robertson pupil with similar reactions (usually bilateral) is often regarded as a sign of syphilis. Six cases (5 ♂ 1 ♀) were described. Moore (1924) had already reported seven cases, including a man of seventy with one dilated pupil, his sister and granddaughter being the same. In 1932 he added eight more cases with Argyll-Robertson (non-luetic) pupils. The age of onset may be at birth, 5, 7, 20, 24 or 42 years. One case lived for forty-seven years after the condition was discovered. Moore concluded that it is not related to syphilis nor to any constitutional or nervous disease. Langworthy and Ortega (1943) describe the innervation of the iris in the albino rabbit and discuss the abnormal pupils in man.

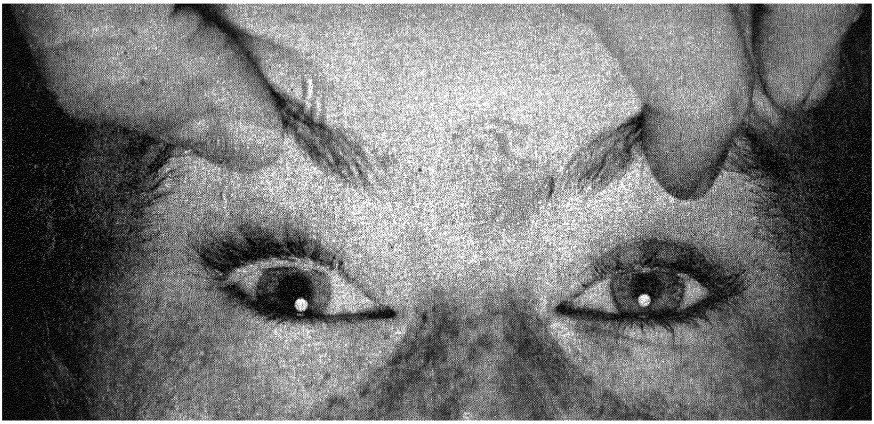

Fig. 65. Adie's syndrome in a girl. Right pupil dilated. (From photograph by Dr. D. G. Cogan)

Rudolf (1936) reported the condition in mother and daughter. Dressler (1937) found it in three sisters, the parents being normal. A son and daughter of one, an aunt and a cousin on the father's side, had *hippus* (spasmodic alteration of pupil-size or tremor of iris). The three sisters had both. Dressler thought the condition recessive, but it seems more like a conditional dominant. Scheie (1940) reported six more cases and postulated the lesion as a partial parasympathetic denervation peripheral to the ciliary ganglion. McKinney and Frocht (1940) describe 7 cases (3♂ 4♀), including a father and son, and discuss the etiology. This is another inherited condition of the sympathetic nervous system, probably an irregular dominant of low penetrance, not uncommon and much more frequent in females than males.

White and Fulton (1937) describe a case of adult female identical twins with both pupils showing dilation and oval shape, reacting to constricting stimuli only in two quadrants. The same condition was present in the mother but absent from five children of the twins and five sibs. It is probably an irregular dominant. A case of myotonic pupil was known as early as 1813.

Border of Pupil

The edge of the pupillary border (saum) is an interesting structure, microscopic in dimensions yet showing inherited differences. The normal appearance is shown in Fig. 66. It is composed of dark brown lobes separated or close together according to whether the pupil is open or closed. Vogt (1923) showed that this border in man may be double, single, absent or with cysts. *Flocculi*, i.e., wart-like excrescences, may form on the margin (Fig. 67). A double pupillary margin was found in two brothers. Vogt, who showed that flocculus-formation of the pupil margin is also hereditary, has made some illustrated studies of this subject. In diabetes the margin is not much altered, but senile changes make it discontinuous. Hyaline changes are also

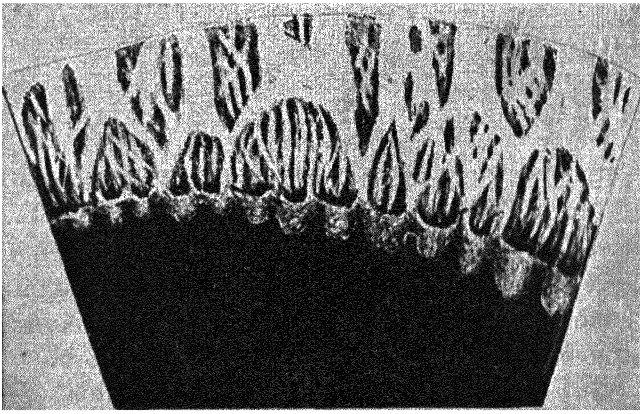

Fig. 66. Normal pupillary margin, showing nodules separated in open pupil. (After Waardenburg)

regarded as senile. Cysts are not rare. With iridocyclitis (inflammation of the iris) there is a typical efflorescence. With hereditary dominant glaucoma, glassy round excrescences appear on the border. The flocculi have been regarded as atavistic in nature, as they are present in many fishes and amphibians. They are formed particularly on the upper border of the pupil. Vogt distinguished lamellar and tuberose forms. They occur in horses, but not in dogs, cats or pigs. Froelich (1924) published seven pedigrees of flocculus-formation without certainly determining the method of inheritance. Waardenburg (1932) found fourteen men and fifteen women with flocculi, although the earlier observations indicated an excess of males with the character. All the evidence indicates that it is an irregular dominant. Måhlén (1942) describes a very marked case of bilateral flocculi in a boy and confirms their greater frequency in males.

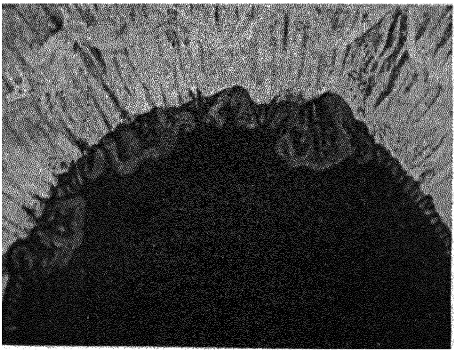
Fig. 67. Flocculi on margin of (closed) pupil. (From Waardenburg after Vog')

The *Iris* is thicker and more heavily pigmented in Negroes. *Hyperplasia* or partial doubling of the mesodermal tissues of the iris is inherited as a dominant condition. *Split iris* (in two layers) was recorded by Waardenburg in a mother and three children. *Hypoplasia of the stroma* is a recessive sex-linked condition with secondary glaucoma. Dominant forms of this condition have been reported by several authors. In some families it is combined with other ocular defects. *Hypoplasia of the iris dilator* muscle has been seen in sibs in certain cases. *Polykory* (two to five pupils) is a rare condition which shows signs of inheritance.

Aniridia

Defects of the iris and the lens of the eye furnish a large proportion of the inmates of blind schools. When the inheritance of these conditions is understood by doctors and patients there should be a slackening in the serious increase of blindness through inheritance, for those who would transmit blindness should obviously be advised to refrain from reproduction.

Aniridia, or absence of the iris, has been described in several pedigrees cited by Macklin (1927d). A trace of the iris always remains. Cunningham records aniridia in four generations of a family as a simple dominant skipping one generation. In various pedigrees it is combined as a dominant with other eye defects. Coloboma and aniridia are interchangeable; both may occur in the same person and a parent with one condition may have children with the other. Aniridia is equivalent to total coloboma. Ingrowth of the iris fails owing to the persistence of the irido-hyoid blood vessels. These normally appear at the fifth week and begin to disappear at the middle of the third month, when the ectodermal part of the iris is starting to grow forward over the front of the lens. Sedgwick (1861) described cases of the inheritance of aniridia. Duggan and Nanavati (1927a) cite a case where all four children of a third wife were affected, the previous children of the father being free. The mother had nystagmus, bad sight and probably aniridia. Rush (1926) described another family with congenital aniridia.

Partial aniridia is also dominant, Polte's family having seven cases in three generations. Many other pedigrees are referred to by Waardenburg (1932). Neher (1938) describes a family with dominant congenital aniridia in five generations, 15 cases (10♂ 5♀).

There are various inherited anomalies of the *tear-sac and duct.* Poljak and Popova (1929) described two Russian families with *inflammation of the tear-sac*, inheritance dominant. In one there was a congenital nasal fistula (nine members in four generations); in the other the lesion occurred at about twenty-five years of age (three cases in three generations). Displacement of the tear ducts, lack of secretion and atresia of the tear ducts are also inherited, generally as irregular dominant conditions. Schnyder (1920) described a family with six cases of tear-duct defects in three generations.

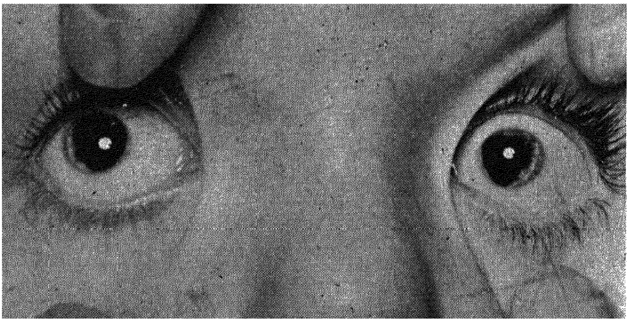

Fig. 68. Extreme coloboma of iris in both eyes. The pupils were dilated by a mydriatic. (From photograph by Dr. D. G. Cogan)

Coloboma is a congenital fissure which may appear in any part of the eye, as the iris, choroid, lens, vitreous or eyelid, through failure to complete development. *Coloboma of the iris* (Fig. 68) is not uncommon and is generally a somewhat irregular dominant. The family of Snell (1908) has 14 cases (6♂ 8♀) of bilateral coloboma of the iris in five generations, strictly dominant, sibships 14 affected : 13 normal. The three infants in the last generation showed aniridia. Figure 69 shows a family with seven cases, all males, in three generations, III. 7 having the defect in one eye only. This is probably an irregular dominant; it might be sex-linked, but the inheritance is also direct from father to son. This pedigree could be explained by crossing-over between the X- and Y-chromosomes. *Coloboma lentis* with ectopia lentis was followed in four generations (five cases) by Clark and in three generations by Bahr as an irregular dominant. Davenport (1927b) described macular coloboma as a gap in the choroid, occurring in mother and son. DeHaas (1931) found it in a father and three sons, two daughters and one son being normal.

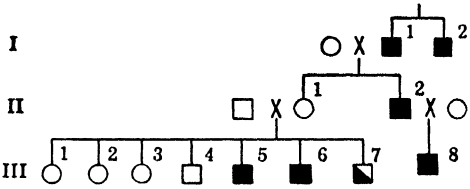

Fig. 69. Pedigree of coloboma iridis. (After Sedgwick)

Coloboma of the macula together with apical dystrophy of hands and feet was described by Sorsby (1935) in a mother and five of seven children. The mother's parents and ten sibs were all normal, so she was probably an original mutation. The coloboma was bilateral and pigmented. The nails on the index fingers and big toes were rudimentary and there was a tendency to complete bifurcation of the thumb and big toe. One boy had also a single kidney. Probably two linked genes are involved, the apical dystrophy being of the type described by MacArthur and McCullough. It appears probable that the eye defect and the skeletal defect were separate mutations, arising together in the same chromosome in one of the germ cells that produced the mother. If in homologous chromosomes, they would be in the repulsion phase in the offspring. The alternative is one mutation with multiple effects. Halbertsma (1932) gives six short pedigrees indicating that coloboma of the macula is an irregular dominant arising early in development, while a hole in the macula arising much later is always unilateral and is probably not inherited.

An experimental study of coloboma in creeper chick embryos by Gayer (1942) throws light on their origin. He produced this condition by transplantation of a normal optic vesicle to the flank of the chick. Every such grafted normal eye rudiment developed a coloboma similar to that found in the eyes of phocomelic creeper chicks. He concludes that extrinsic factors outside the cup play a part. This does not necessarily always follow, however, for it is well known that in many features of development extrinsic and intrinsic factors can produce identical results. In other words, there are many instances where a gene mutation produces the same effect as an environmental stimulus, so there is no contradiction involved in finding the same condition produced genically in one case and by an extrinsic factor in another.

Gesell and Blake (1936) have made a full study of a pair of MZ female twins 12 years of age, both having bilateral macular coloboma. The similarity extended even to the virtual duplication of the position, size, outline and pigmentation of the coloboma in all four eyes. They discuss the heredity from an embryological point of view and give full references to the literature, besides analyzing the various studies of ocular abnormalities in MZ twins.

Myopia and Hyperopia

Normal sight, in contrast to long- or short-sightedness, is a complex condition (emmetropia) in which the light rays are focussed exactly on the retina. This depends especially on the axial length of the lens and the refractive index of the cornea, but to a small degree on various other adjustable features of the eye, such as the position of the lens and the refractive indices of the media in the various chambers of the eye. Children are born hypermetropic (long-sighted) and normal sight or myopia arise later. The observations of Hermann Cohn on school children in Breslau in 1867 made it appear that myopia arose through faulty lighting in schools.

When apes in Java were kept in a horizontal position so that the eyes were subjected to venous engorgement, five out of seven became myopic while the controls were unchanged. Keith (1925) attributed myopia to a disorder of growth, a faulty reaction of the fibroblasts of the sclerotic to the strain they are subjected to arising from intraocular pressure during the period of growth. He suggested that prolonged stooping over a desk would increase this effect, as in the apes. Clarke (1925) regarded the condition as one of stretching of the fibroblasts in the very early growth, and thinks the interpupillary distance is greater in myopes. He estimated that by the sixth year one child in 1000 is myopic, whereas at twenty years the frequency is 15 per cent, and in Germany even higher. Von Verschuer (1930) finds that it ranges from 24.5 per cent in Schleswig-Holstein to 41.8 per cent in Upper Bavaria. Sir John Parsons regards congenital weakness of the sclerotic as the inherited factor, the sclera being easily misshapen by use. Eldridge-Green found that continuous lifting of heavy weights, which causes engorgement of the eye, produced myopia; but it was pointed out that this could only be when a weak sclerotic was already present, otherwise every athlete and coal heaver would be myopic.

Steiger, in earlier studies of 50,000 eyes, emphasized the hereditary factor in myopia. Studies of Nordgren (1936) and others have shown that in Sweden myopia has declined in frequency about one-third between the years 1894 and 1920 but there has been little reduction since. School hygiene has improved during this period, but the incidence of myopia had no relation to life in town or country, nor was myopia associated with poor physique. There was a positive correlation with conditions of nutrition. Evidently predisposition and external circumstances both play a part. Wilson (1935) collected 1500 consecutive cases of myopia in England and investigated their family history. Where the father or mother was myopic they transmitted myopia to two girls for one boy. Among over 22,000 school children with defective vision 57.9 per cent were girls. At ages 7 to 10 years there were 4.6 hypermetropic to one myopic, but at 15 to 17 years the ratio was 1 : 1.

Hypermetropia, the congenital condition, is shown (Waardenburg, 1932) to be a somewhat irregular dominant in many families. The highest grade of hyperopia is recessive and generally associated with microcornea, microphthalmus and blepharophimosis. The heterozygous condition is intermediate. In 84 families with 453 children there were 149 hyperopic — always more than 2 diopters. In two families astigmatism was also present and was separately inherited (Fig. 70), two children of the third generation showing each condition in one eye. The other family shows that a person with astigmatism only can transmit both astigmatism and hyperopia. Lambert and McDonnald (1931) found a family in which the mother and four of seven children had a high degree of farsightedness.

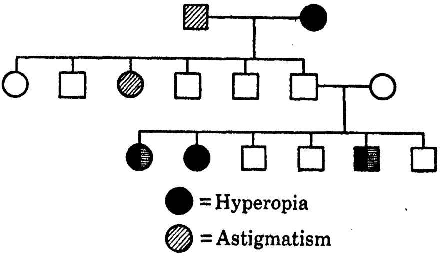

Fig. 70. Pedigree of hyperopia and astigmatism. (After Waardenburg)

Myopia also exists in many grades. Waardenburg (1932) cites *infantile myopia* as a separate condition, twice as frequent in boys as girls, distinguished by deeper pigmentation of the macula while the rest of the fundus is often weakly pigmented. Strong myopia is generally recessive, as in the family (Fig. 71) of Jablonski (1922). Waardenburg concludes that there are several biotypes of high-grade myopia, having found a case in which two such myopics had a normal daughter. Czellitzer (1912) collected over 1000 pedigrees of high-grade myopia. In one family with a myopic mother, six of the seven children were myopic, one of them unilaterally, indicating failure of penetrance on one side. Gassler (1925) described a family with ten cases in two generations of axial myopia combined with excessive and probably congenital night-blindness, and convergent strabismus. The myopia was 9–16 diopters. The inheritance was recessive and accompanied by a very high infant mortality. Another family shows that the association of myopia and hemeralopia is not complete.

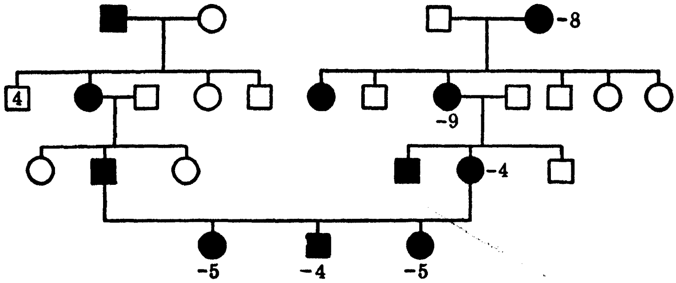

Fig. 71. Pedigree of recessive myopia. The figures indicate the number of diopters. (After Jablonski)

Studies of identical twins show that the range of variation in refraction for any genetic condition is a narrow one. That myopia can be strictly recessive sex-linked is shown by an early pedigree (Fig. 72) of Worth (1906). The myopia was 10–12 diopters, with some astigmatism. It is stated that in this family all the myopic (males) had brown eyes while all the normals had blue eyes. Search should be made for linkage between myopia and eye color. Another pedigree of sex-linked myopia is by Oswald (1911), with five males affected in four generations. Yamazaki (1927), from a study of 1906 families,

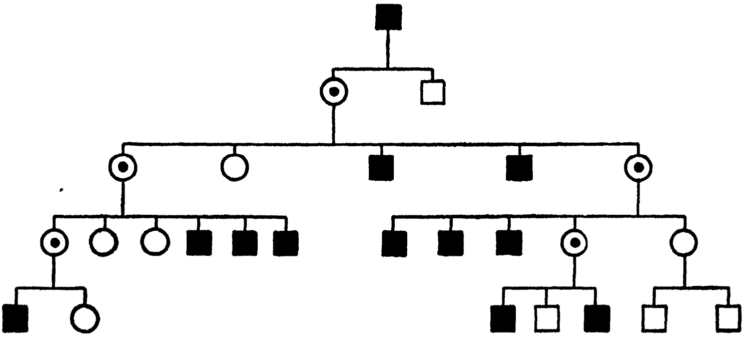

Fig. 72. Pedigree of recessive sex-linked myopia. (After Worth)

regarded high-grade myopia as the homozygous and low-grade as the heterozygous condition.

Waardenburg (1932) found an interesting family in which a hyperopic man married a myopic woman. Two of the girls were emmetropic, two boys myopic and one daughter hyperopic. This result could be explained through incomplete dominance or polymeric or allelic inheritance of the genes for long and short sight. Myopia develops particularly during puberty and prepuberty, so the increase in the optic axis may possibly have hormonal connections.

Czellitzer (1928), Vogt and others have assumed two genes to explain myopia. Moderate degrees of the condition seem to show intermediacy in inheritance, which may indicate a polygenic condition. It is probable that axial length of lens and corneal curvature are independently inherited, as Vogt suggested. This would be analogous with the independence of cataract of the cornea and lens. Vogt described one family with dominant myopia, weak sight and nystagmus but not albinotic. In a family of Waardenburg (1935) these conditions could separate. He suggests that the correlation of myopia (lengthening of axis) and intellectual ability is more intelligible since they have a common (ectodermal) basis. Many albinos are myopic, while those with coloboma and aniridia are mentally abnormal. Farsightedness (short axis) is frequent in the feebleminded and mongoloids.

Liepin (1924) found that in marriages between emmetropic parents who had myopic children the numbers were 166 normal : 52 myopic, which is close to 3 : 1. When both parents were myopic all the children were so. Monohybrid recessive is then the usual method of inheritance of myopia, especially as regards high-grade conditions, but some results do not fit this simple scheme. Probably there is a gene with irregular dominance in some families. Otherwise a relatively high incidence of recessive genes in the population must be assumed. These problems can only be solved by a fuller and more accurate study of myopic families.

Flach (1942) publishes a peculiar pedigree with 23 cases (3 ♂ 20 ♀) of myopia in three generations, 5 of them (2 ♂ 3 ♀) being low grade. Normal parents had four normal sons and three daughters with high-grade myopia. The sibships number about 23 affected : 27 normal and the inheritance is probably autosomal, irregularly dominant, but with a great excess of affected females, making it almost sex-limited.

Myopia is a condition which tends to accumulate in civilization. It also occurs in rabbits, horses and monkeys under domestication, but natural selection presumably eliminates it under wild conditions.

The refraction curve for the population is asymmetrical, myopia being much more frequent than hyperopia. The curve for high-grade myopia is also irregular, indicating different types of myopia, some of which may be dominant.

Anisometropia is a condition of unequal refraction in the two eyes. Certain records show that one-sided heredity can occur. Blatt (1924a) referred to two sisters with right eyes emmetropic but left highly myopic (21–22 diopters). A daughter of one showed 2 diopters in the right eye and 25 in the left. All three showed some abnormality in the left eye. In another case (Passow) the father, son and daughter were all myopic in the right eye, with respectively 17, 20 and 3 diopters, the left eye being normal. Three brothers (Wessely) had congenital atresia of the right nasolacrimal duct.

Cataract

Cataract is a condition of the lens in which certain parts or the whole become turbid instead of transparent to light. Cataract may be congenital, it rarely occurs in early childhood, may develop in middle life, and senile cataract occurs frequently in old age. These are all independent entities which can be traced in different families. The inheritance is nearly always dominant, but certain recessive pedigrees are known and in at least one family it is sex-linked.

Much is being learned regarding the chemical pathology of cataract as a series of steps in the chain of causation. Campbell (1933) states that the lens contains a specific protein, γ-crystallin. β-crystallin is also abundant, but decreases with age. They are rich in the amino-acids cystein, tyrosine and leucine. The lens is also rich in potassium but poor in calcium and there is a sulphydryl compound usually identified with glutathione. In cataract formation, striae and fluid vacuoles develop and the lens fibres become opaque, the proteins diminish, the calcium increases and the potassium almost disappears. The sodium and chlorine, and later the cholesterol, increase. When the cataract is mature the lens has lost its glutathione. Sudden changes in the blood sugar, in diabetes, produce changes in refraction of the lens, and it is well known that cataract may develop in connection with diabetes. Bücklers (1939) observed a star-shaped cataract in a man of fifty at the beginning of treatment for diabetes. It regressed in a few weeks and at the same time transitory hyperopia appeared. Both were attributed to an excessive intake of water by the lens.

Probably the first change in the origin of cataract is in the permeability of the lens capsule (envelope). It is normally permeable to water, electrolytes, sugar and small colloidal particles, but impermeable to glutathione, albumen, globulin and proteins of high molecular weight. A decrease in permeability may begin senile cataract; later it becomes so permeable that the proteins escape. The opacity which develops is due to the precipitation of the lens proteins. Increase of calcium precipitates α-crystallin in the lens. The cataracts produced in rabbits by naphthalene are most like senile cataract in man. Campbell (1936) has since stated that excess of sugar, deficiency of vitamins, disturbance of the calcium metabolism or loss of cystine from the lens are all very likely factors in the causation of cataract. Campbell found cataract recessive in rats.

Szily and Eckstein (1923) showed that lamellar cataract can be produced in suckling rats by feeding the mother on a diet deficient in vitamin P and fats. Mitchell and Dodge (1935) found that when rats are fed on lactose 68 per cent of them develop cataract, but starch, maltose, dextrin or sucrose produce no such effect. Galactose will also produce cataract in rats and rabbits. The calcium content of cataractous eyes was double the normal, but there was no increase in the calcium content of the blood or bones. Lack of vitamin A has produced cataract in puppies, while lack of B_2 (G) will produce it in rabbits and rats. It is now known that "slimming" substances, such as naphthalene and dinitrophenol, produce cataract, so that their use is dangerous. Josephson *et al.* (1936) state that a woman exposed to naphthalene gave birth to twins, one with no eyes and the other with one microphthalmic eye, both without ears and with bony hypertrophy, one with enlarged nose. Kusagawa found that in chicks naphthalene not only causes cataracts but he claims that the toxic effects were inherited by successive generations. Dinitrophenol produced the same deformities in chicks.

Tryptophane deficiency causes cataract in rats, as well as vascularization of the cornea, alopecia, defective incisors and atrophy of the testis. In addition to diabetic cataract, there is a form associated with tetany and a third connected with myotonic dystrophy, atopic eczema, riboflavin deficiency, etc. Nachtsheim and Gürich (1939) describe a hereditary juvenile cataract (in both eyes) in rabbits, which is a simple Mendelian recessive. The vitality is not decreased. Turbidity in the lens is visible with the eye mirror and slit lamp in the third week after birth. Lamellar cloudiness begins in six to eight weeks and is soon followed by clouding of the centre of the lens. It finally becomes visible to the naked eye and occupies nearly the whole lens, but new layers added to the lens by apposition are free from turbidity. In some cases the cataract develops much more slowly, requiring a year or more. Smith and Barrentine (1943) describe a dominant complete bilateral cataract developing in a strain of rats a few days after birth.

In man, many different types of cataract are known and named, depending on the pattern of the turbidity and the time of its development, such as C. senilis, praesenilis, coronaria, diffusa posterior praesenilis and punctata, zonularis, coralliformis, stellata, nuclearis pulverulenta, totalis congenita. Their specificity in development and inheritance is remarkable, and Vogt claims to be able to distinguish dozens of different types, each characteristic of a family; but in many families the development is rapid and very similar. In some types of cataract crystals develop and these may be composed of cholesterin, tyrosine, leucine, calcium sulphate or calcium oxalate. Romer (1926) described a family with ten cases of dominant spiess (spear) cataract in four generations. Masses of needle-like crystals (partly cholesterin) appear in the lens.

As regards age of development, Tatham (1890) described a remarkable family in which the senile type of cataract developed at three to five years. The pedigree contained 11 cases (6♂ 5♀) in four generations and was strictly dominant, appearing in both eyes, the earliest cataract beginning in one eye at seven months. Another striking pedigree is that of the Coppock family near Oxford (Nettleship and Ogilvie, 1906). There are six generations of descendants from John Coppock, born in 1774, and in the last four generations 18 cases (9♂ 9♀) of a peculiar form of cataract which is strictly dominant. It is very partial and circumscribed, sometimes so slight that the patient is unaware of any imperfection. The opacity is in the form of a sharply defined circular disc deep in the lens. It is stationary and may be seen as early as ten years or as late as eighty-two. The family is of high intelligence.

Stieren (1907) described an early case of recessive sex-linked cataract. In three generations fifteen males were affected. They were born blind, none of them married and nearly all died in infancy. In addition, five other boys and two girls died young, so it would appear that this cataract was associated with a sublethal effect.

Harman (1909) published a pedigree of dominant cataract with nineteen cases in five generations, and later (1910) summarized all the earlier literature, classifying cataracts as lamellar, axial, stellate or polar according to the position and character of the turbid area.

Danforth (1914) described the work of von Szily in mating a cataractous male rabbit with a normal female and finding cataract in the rabbit embryos. It was traced to a group of cells in the lens cavity, which proliferate for a time and then degenerate, setting up degeneration in the surrounding lens tissue. Von Szily also found that in certain chick embryos a fold of the amnion was enclosed in the lens cavity, and suggested that this is the probable origin of the cataract. Since it is known that the lens of the eye is produced under the stimulus of the optic cup, any aberration in the stimulus might cause a defective lens.

In Danforth's human pedigree (Fig. 73) the condition appears uniform as lamellar cataract together with defective retina, and is dominant, with 9 cases (4♂ 5♀) in three generations. The original mother was normal, so the condition appears to have originated *de novo*. The original father had several children, all normal, by a first wife, while his second wife, who was also normal, had one cataractous child from which the descent arises. If the condition originated with the father it must have been only in his later germ cells. Nystagmus and slight mental deficiency were also noticed in this family. The condition might have been recessive, carried by I. 2 and I. 3. But the large number of affected children in generation IV is not accounted for unless III. 10 is a carrier. Danforth points out a tendency for abnormalities to accumulate in a pedigree through the intermarriage of those having different defects. In some cases this tends to the ultimate elimination of the defective stock.

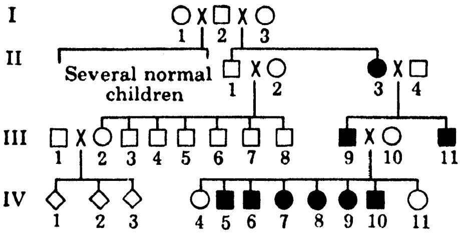

Fig. 73. Pedigree of dominant cataract. (After Danforth)

Garfunkel (1926), in a study of *senile cataract,* points out that it can be traced back to the eighteenth century, but a man may transmit it and die too young to show it himself. The pedigrees of twenty-nine patients were investigated. In twelve of them the condition accumulated in the pedigree, and the inheritance was dominant; while in seventeen only single cases occurred, and the condition was either recessive, mutational or induced. Thus the controversy as to whether cataract was dominant or recessive is settled by both types of inheritance occurring in different pedigrees. Only persons reaching sixty years of age are entered in the pedigrees. In the 12 families there were 110 members over sixty years of age. Of these 49 were cataractous and 61 free. Adding to the former 8 others under sixty, we have a total of 57 : 61, which agrees with a ratio of 1 : 1. It is found that cataractous families in general reach older age than normal families. Khan (1926) gives a short pedigree of dominant lamellar cataract in three generations.

Halbertsma (1928) described two pedigrees of *juvenile cataract.* In one, forty-nine members of a family in three generations had cataract, the principal types being cataracta coerulea punctata anterior and posterior perinuclear zonular cataract. In another family near Delft there were ninety-five persons in the pedigree, and the inheritance was clearly dominant. In one family in the fourth generation of this pedigree both parents were affected and seven of their nine children. This is in accord with the (3 : 1) expectation where both parents are heterozygous. Another fourth generation family with one parent affected had seven children, all affected. This is probably not merely the chance departure from a 1 : 1 ratio. Manson

(1928) gives a pedigree in which congenital lamellar cataract is dominant, with seventeen cases in four generations. The same pedigree shows three cases of a digital abnormality, the little fingers being bent outward at the lower joint. The eye colors of the members of this pedigree were also examined. Of the cataractous, 7 had brown eyes, 2 gray with brown around the pupil, 4 gray = 9 : 4. Of the 12 with normal lenses, 3 had brown eyes, 2 gray with brown around the pupil, and 7 gray (including 1 light blue) = 5 : 7. Hence there was probably no linkage between cataract and eye color.

Huber's (1935) pedigree of *senile cataract* is from the isolated village of Elm in Switzerland where there has been much inbreeding. There were 16 cases (10 ♂ 6 ♀) in three generations and the inheritance is either recessive or a dominant of low penetrance, the sibships numbering 16 affected: 25 normal. Two in the last generation show myotonic dystrophy (*q.v.*). Lamellar cataract occurred as a dominant in 5 generations (Galloway, 1930) with 21 cases (8 ♂ 13 ♀) and no skip, the sibships showing 20 with cataract : 18 normal.

Hornbach and de Garis (1933) published an extensive pedigree of cataract with 34 cases (16 ♂ 18 ♀) in five generations. It began with a cousin marriage, but this had no effect on the inheritance, which was dominant and transmitted only by the affected cousin. Operations for cataract were performed from ages seven to sixty years, the mean age being 25.9 years. Omitting the last generation, many of whom were young, the sibships number 30 affected : 35 normal, thus showing that a single dominant gene is involved. There were two skips, or failures of penetrance, in the third generation, but these two men transmitted the condition just as strongly as those who developed cataract.

Halbertsma (1934) published a pedigree of dominant congenital cataract with 12 cases (10 ♂ 2 ♀) in four generations. Two cataractous brothers had also heterochromia iridis (Fuchs' congenital form). Hoffmans (1936) recorded 8 cases (5 ♂ 3 ♀) in three generations, the onset of cataract at about twenty years of age. In dominant cataract the sex-ratio is about 3 ♂ : 2 ♀.

There were two peculiar pedigrees in Harman's (1910) collection. One is Dyer's case, 1846, in which six males only were affected in four generations. This might be interpreted as male-to-male inheritance through the Y-chromosome, but as there were only three female sibs in the pedigree and none of them had children the evidence for this interpretation is not very strong. The other is Galezowski's case, 1882, in which there were seven affected, all females, in four generations. This may be a case of attached X-chromosomes ($\widehat{XX}$) as the transmission is only female-to-female. But it might be only the chance result of an ordinary dominant gene, as there are but two male sibs in the pedigree.

Bücklers (1932) published two cases of probably recessive cataract of a new form in which consanguinity was involved. The pulverulenta type (Vogt) was surrounded by fibre-like structures.

Macklin (1927) states that 13 per cent of the pupils in blind schools are blind through cataract. They should obviously not have children, especially in lines of descent in which the disease is dominant. She cites many pedigrees from the literature, including coralliform cataract by Fisher and by Nettleship, presenile cataract by Davenport and by Nettleship, lamellar by Nettleship, posterior polar by Ziegler and Griscom, zonular by Derby, discoid or Coppock cataract by Nettleship, Chance, Dorell, senile cataract by Green, Nettleship, Dickey, Brown. In all cases it is a Mendelian dominant with the type fairly constant in each pedigree. A pedigree of Nettleship showed two skips, but these might have developed cataract in their old age.

Keeler (1934) pointed out the need for examining the inheritance of all inmates of blind schools. Their blindness results in many cases from cataract or optic atrophy. He showed that in five pedigrees of dominant congenital cataract, five blind progenitors produced a total of sixty-eight congenitally blind descendants in three or four generations. He suggested that the blind should themselves propose laws to prevent the reproduction of hereditary blindness, but surely this is a matter of sufficient urgency for intervention by the State.

In all hereditary eye diseases (and others as well) many single cases are observed (with normal relatives and ancestors) for each one with a family history. Usher (1933) discusses the origin of such cases and favors the view that they are recessive Mendelian outcrops. In the case of such strongly dominant conditions as cataract some must be gene mutations. Figure 74, from Usher, may represent such a case.

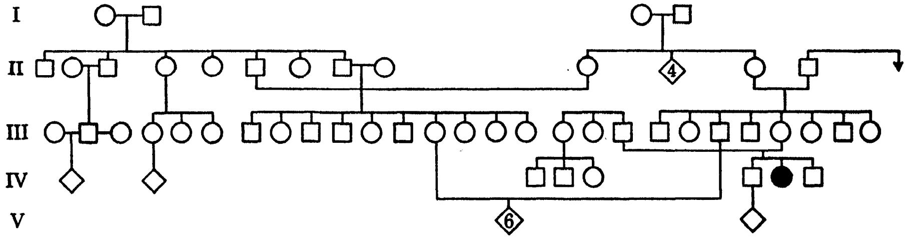

Fig. 74. Probable origin of cataract by mutation. Many other normal ancestors were omitted. (Modified after Usher)

Manson (1912) described a pedigree of lamellar cataract with thirteen cases in four generations transmitted through affected females. The first case was a female with normal relatives, who may have been a mutation.

Anticipation has often been discussed in connection with cataract. In view of the evidence for its possible existence in certain other diseases, I agree with the statement of Nettleship (1909). He said, "It appears to me that the subject of anticipation deserves much more attention than it has received in relation to theories of heredity and the origin and extinction of heritable conditions." Vinsonhaler and Cosgrove (1936) describe senile and pre-senile cataract in a family with 22 cases (10♂ 12♀) in six generations. The inheritance is dominant, without a skip, and the sibships number 19 affected : 17 normal. The anticipation in this family can hardly be ascribed to chance. In the second generation, cataract developed at seventy, and in each succeeding generation the age of onset decreased one decade. The sixth generation shows lenticular opacities at twenty-seven years. If this continues, the tenth or eleventh generation should have congenital cataract.

Vogt (1938), a great authority on cataract, finds the many forms very specific. Spear cataract, previously unknown, was found by him, inherited as a dominant in the canton of Neuchatel. C. centralis pulverulenta is in the centre of the lens, C. congenita nuclearis, sharply distinguished from all others, is found in a single family in Zürich. Other stationary types are C. pisciformis and anterior axial embryonal cataract. Senile cataracts, which are much more frequent, also occur in a variety of inherited forms: coronaria, radial, cuneiform, lamellar fissure, nuclear, and total sclerosis with subcapsular cataract. Unlike congenital cataracts, the senile ones are progressive, the rate varying greatly in different types. Their inheritance is shown by the study of senile identical twins. Lutman and Neel (1945) describe a pedigree in which different types of cataract occur in the descendants of one person. Enriques' (1922) pedigree of senile cataract is believed hologynic.

Kugelberg (1934) points out that the skin diseases scleroderma and neurodermatitis are so often described with cataract that there must be some connection between them. Cataract has also been described with other rare skin diseases. He cites a recessive pedigree with eight cases in two generations from related parents, six of them showing both scleroderma and cataract, one cataract only and one scleroderma only. Both these skin diseases are often of endocrine origin, especially from the thyroid and sex glands, so the same hereditary disposition may account for both the skin and eye conditions. The type of cataract with both skin diseases is very similar and different from other types, so it is called *c. syndermatotica.* Werner (1928) cites a Finnish family in which the father had cataract and curly hair, the mother good eyes and straight hair. Three sons are like their father, two sons and three daughters like their mother in these two characters. This dominant cataract is therefore probably linked with the gene for curly hair, which appears to be recessive. Five others in the pedigree had only curly hair.

In connection with a severe epidemic of rubella (German measles) in Australia, Gregg (Swan *et al.* 1943) reported 78 cases of cataract of peculiar type in the child, when the mother had rubella in the first three months of pregnancy. The cataract was of dense nuclear type, generally bilateral. Many of the babies were small, 44 had congenital heart lesions. Some also showed microphthalmia, microcephaly and deaf mutism. The virus evidently penetrated the placenta and produced the lesions in the embryonic tissues. Greenthal (1945) reports two such cases in the United States. In one the infant was congenitally deaf. The other infant had congenital cataract with mental retardation and probably a heart malformation. For later papers see *Lancet* 249 : 19.1945. Long and Danielson (1945) report six more cases. Three babies had bilateral cataract associated with bilateral microphthalmia, three had lesions of the fundus and all had cardiac defects.

Hippel (1930) bred together two shepherd dogs blind from cataract. From various matings sixteen dogs with cataract were obtained, the dominance being perhaps incomplete, and the embryological development of this congenital cataract was studied. The lens was at first normal but later became most cloudy in the middle. It is lamellar, but not sharply delimited as in men. The first pathological changes take place in the capsule but it is different from capsular cataract in man. Bourne and Grüneberg (1939) describe cataract in rats associated with retinal degeneration. In this mutation, traces of the hyaloid artery, which normally disappears in development after forming a network on the posterior capsule of the lens, remain. A stippling of opaque dots near the posterior pole of the lens may be followed by complete opacity. In some rats homozygous for this recessive gene, instead of cataract the epithelium at the back of the lens undergoes changes so that ophthalmological examination shows yellow, green, blue and finally "shagreen" reflections. A number of homozygotes are "normal overlaps," showing neither cataract nor shagreen nor a persistent hyaloid. These, however, retain a characteristic degeneration of the retina which is regarded as the primary genic effect. This primary effect is perfectly inherited whereas the other effects are irregular in occurrence. In a histological study of this strain, Bourne, Campbell and Tansley (1938) found that the retina develops normally for seventeen days. Then disintegration of the rods takes place, then the cones, next the outer nuclear layer, followed by the inner nuclear layer and finally by cataract. They regard the course of events as supporting the view that retinitis pigmentosa is primarily a degeneration of the neuro-epithelium rather than a disease of the choroidal vessels.

Detlefsen and Yapp (1920) described a case of congenital cataract in cattle, which behaves as a simple recessive. A registered Holstein-Friesian bull inbred with his own stock gave a number of cataractous offspring. There is no record of cataract in any of the ascendants. To unrelated cows this bull produced only normal calves. But thirty-two F_1 daughters mated to an F_1 son gave sixty-three calves, fifty-five of which were normal and eight had congenital cataract of the stellate type. An apparently identical recessive defect is described in Jersey cattle by Gregory, Mead and Regan (1943). The cataract is congenital, at first perinuclear, with opaque lens and impaired vision. The eyes may also be reduced in size, the cornea is often distended and the lens more or less displaced.

Persistent hyaloid artery is a rare condition in the human eye. This artery grows in from the optic nerve end, through the vitreous to the lens during development. Fragments of it may persist on the posterior wall of the lens. Ivanov (1928) found this condition bilateral in a father, two sons and two daughters, unilateral in another daughter. It appears to be this structure, greatly developed, which forms the pecten in the fundus of birds and reptiles (see Wood, 1917).

Many inherited abnormalities of the retina are known. Mann (1935) describes the embryological origin of *congenital retinal fold* (ablatio falciformis) from six cases with eight affected eyes. Weve (1935) found the condition in fourteen eyes of eight patients belonging to four families. It occurs in different grades, the bilateral cases being symmetrical, accompanied by nystagmus, very good sight and frequently convergent strabismus. The inheritance is probably recessive.

Choroideremia or absence of the choroid is very rare. It was described by Mauthner in 1872. It produces a form of night-blindness. Usher (1935b) found twenty-two cases reported, all but one in males and all single cases, except three families in each of which there were two affected brothers. In some families with choroideremia other forms of night-blindness are present, others are accompanied by retinitis pigmentosa. A pedigree of choroidal atrophy with pigmentary degeneration of the retina shows dominant inheritance with 13 cases (7 ♂ 6 ♀) in three generations. Niccol (1938) described a brother and sister with gross bilateral defects of the choroid at the macula. The vision was good and intelligence normal. The parents were unrelated but in the mother's eyes the macula was stippled with light yellow specks like gold-dust. Verhoeff (1942) concludes that most cases of "choroideremia" are really examples of retinitis pigmentosa in which the choroid is not absent but hidden by widespread gliosis (overgrowth) of the degenerating neuroepithelial layer of the retina. Goedblad (1942) finds that in choroideremia, the fundus (except the optic disc and macula) is grayish or greenish white, due to absence of the pigment layer of retina and choroid. He found only thirty-four cases recorded. He regards the condition as sex-linked, heterozygous females having a "pepper and salt" appearance of the fundus. Waardenburg (1942) recognizes two types, both in the X-chromosome: (1) is infantile and recessive, (2) is juvenile, less extreme, and intermediate to dominant.

Franceschetti and Klein (1941) traced a family through fifteen generations from Ludwig Glaser, born in 1510, with many cases of Friedreich's ataxia, degeneration of the macula, labyrinthine hardness of hearing, schizophrenia, imbecility and epilepsy in later generations, all as recessive conditions except hardness of hearing, which is dominant. They suggest that in this pedigree hereditary ataxia and macular degeneration may be regarded as alternative phenotypes. The other pedigree traces back to a single couple in the fourteenth generation. Recent generations show 21 cases of Fr. ataxia, 4 of macula degeneration and 8 of dominant labyrinthine hardness of hearing. One family had six cases of recessive cerebellar ataxia in the third and fourth generations and two cases of retinitis pigmentosa in the fifth.

Wright (1935) described a family of Portuguese-Indian descent, the parents unrelated, in which three sons showed *macula degeneration* beginning after the eighth year. A daughter eight years old was normal. The sons had long, extremely narrow and high heads (cephalic index 62, 66, 77), but they were not oxycephalic. The eldest became mentally defective. Macular degeneration may be congenital, infantile, early or late juvenile, senile or presenile in different families. Stargardt in 1909 described progressive degeneration of the macula in two families and afterward in two others. In all these it was recessive. Behr in 1920 described a family with 17 cases (5 ♂ 12 ♀) in four generations, of juvenile macula degeneration, the first case of dominance. Halbertsma in 1927 recorded a Dutch family with sex-linked recessive macular degeneration, 7 cases (♂) in four generations. This family also had six cases of sex-linked color-blindness, all in males who were free from the other defect. There is thus complete repulsion between these two genes, each in an X-chromosome. Degeneration of the macula is thus generally recessive, but occasionally dominant or sex-linked.

Klainguti (1932) recorded a Swiss form of macula degeneration known as *malattia Leventinese*, most like the Tay form. He gives three pedigrees in which it was present in two successive generations and thinks that two linked genes are involved. In one family two brothers married two sisters and seven of the nine children were affected. It is not congenital, but homochronous in development. Huber (1943) records it in three sisters over thirty years old, in a sibship of seven. In this family it is probably recessive.

Absence of the macula together with albinism of the eye was reported by Vogt (1925) in two families as a sex-linked recessive. One family had eight cases (all males) in three generations, the other fourteen cases in five generations. The fundus was more or less albinotic and the iris might be blue or brown but was relatively transparent. Astigmatism is also present in every case. In a third pedigree, nystagmus with myopia and weak sight is a dominant condition with 9 cases (5 ♂ 4 ♀) in four generations. Vogt cites other cases in which absence of the macula is linked with aniridia.

Atrophia gyrata choroideae et retinae was discovered by Fuchs in 1896. The condition resembles retinitis pigmentosa. There is progressive atrophy of the choroid with pigmentary degeneration. The fundus becomes yellowish-white, the sight dim, with night-blindness. Werkle (1931) found a family with 13 cases (7 ♂ 6 ♀) in three generations, dominant. Waardenburg (1932) describes a sex-linked recessive pedigree with ten affected males in three generations. Usher found fourteen published pedigrees of this rare condition with 26 cases (15 ♂ 11 ♀). Its onset is earlier than choroideremia and all but one were night blind. The inheritance is also recessive and consanguinity of the parents is mentioned in five families. Retinitis pigmentosa was also present in two pedigrees and choroideremia in two. Gyrate atrophy is in some respects like an early stage of choroideremia. One case showed the latter condition in the left eye and the former in the right. That they are genically independent is shown by the fact that one is dominant, the other recessive, and there is a great excess of males with choroideremia. In *retinitis punctata albescens* white dots appear around the macula. This is the rarest form of retinitis pigmentosa.

Reddish gray nodules with a mother-of-pearl sheen lying at the end (papille) of the optic nerve were described by Braun (1935) in two families, (1) a mother and two children, (2) a nephew and two uncles, indicating that it is a conditioned dominant.

Another rare condition is the presence in the retina of *opaque white medullated nerve fibres*. This is normal in the Leporidae and in some Marsupials. In the rabbit they form a transverse band across the retina. The occurrence of this condition in man is therefore essentially atavistic. Cockayne (1936) estimates that the incidence cannot be lower than about 1 in 1800 in Europe or 1 in 1500 in Japan. His pedigree (Fig. 75) shows 10 cases (5 ♂ 5 ♀) in two generations. The pedigree of Kiso contained six cases in two generations. It is as yet impossible to determine whether the inheritance is that of a sex-linked dominant or a simple dominant. Kiso's pedigree is more like that of a sex-linked recessive with variable dominance in the female (as in color-blindness). Catsch (1939) studied sixty cases and found an accumulation of abnormalities, nervous and psychological, in forty-five of them. They usually go to the nerve specialist before they reach the eye specialist. Catsch finds the manifestations very variable and thinks the condition probably polymeric, a dominant with low penetrance, less frequent in females. Further evidence is required.

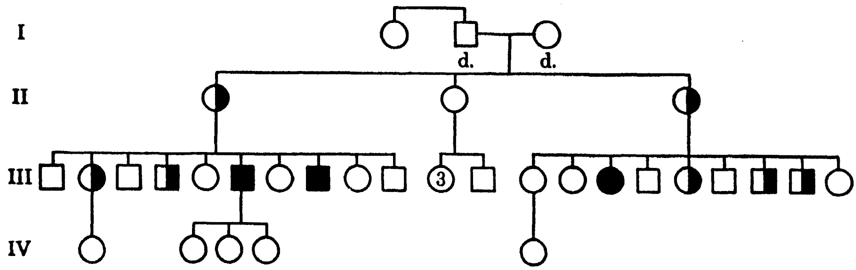

Fig. 75. Pedigree of papilla leporina. (After Cockayne)

Cerebral degeneration with symmetrical changes in the maculae was described in two sisters, seven and ten years old, by Batten (1903). There was a *reddish-black spot at the macula* accompanied by mental degeneration. R. D. Batten reported two brothers, the younger fourteen, with dark pigmentary changes at the macula but no mental defect. They never deteriorated, but each had a central scotoma (blind spot in the retina). Mayou (1904) reported three sibs, a boy of ten and two girls, in the same condition with a reddish-black spot. The intellect began to deteriorate at six years. The parents were first cousins and the mutation is evidently recessive. Many other cases of cerebro-macular degeneration have been described since. Most of these conditions will be considered in Chap. XXIII. Behr described a family with dominant juvenile macular degeneration in 1920 — 16 cases (5 ♂ 11 ♀) in four generations; and the recessive sex-linked form was discovered by Halbertsma in 1927 — eleven males in four generations. Yet other forms occur in families, with onset at different ages from infancy to old age and variations in the type of macular alteration, some of which are illustrated in color by Waardenburg (1932). He later (1936) found hereditary senile degeneration of the macula in three families. Blue (1919) described it in father and son and cites nine other families with affected sibships and normal parents. Steyn (1926) described familial juvenile macular degeneration, and Wright (1935) cited a family in which defective sight appeared in three brothers at ages nine to eleven, associated with progressive mental degeneration and dolichocephaly. A sister and the parents were normal but showed concentric depression of the fields. Two early families of *amaurosis* or hereditary blindness without visible ocular defect were recorded by Sedgwick (1863). In the first the condition was confined to four females who go blind before middle age, the descent direct in three generations. In the second it was restricted to males, with six cases in two generations, a normal father with a blind brother having five blind sons and three normal daughters.

Angioid streaks in the fundus (*retina*) is a rare condition of retinal degeneration. Beginning in 1914, several cases of bilaterally affected sibs were described. Morgan and Batten (1930) gave an account of two brothers and a sister with both fundi showing streaks in the retina. It is a condition of vascular weakness in the eye, leading to hemorrhage and sudden failure of sight, in these cases at *ca.* forty. Then it was described in association with the rare skin disease, pseudoxanthoma elasticum, by Grönblad. Hartung (1932) found this association in two brothers, the parents being second cousins. Five families are now known of angioid streaks alone and five of pseudoxanthoma elasticum alone. They are all recessive. Hagedoorn (1939) reported a case of the two conditions combined, making a detailed histological study. Ebert (1943) agrees that angioid streaks and pseudoxanthoma elasticum constitute a syndrome in which the elastic tissue of the skin, certain parts of the eye and certain arteries are affected. In a family recently observed by Dr. Cogan at the Massachusetts Eye and Ear Infirmary, three adult sons of normal parents had angioid streaks, one of them without symptoms.

Retinal detachment may result from an injury but can also arise through inheritance, being secondary to other conditions. According to Macklin (1927e) it can be dominant, recessive or sex-linked. Later papers are given by Waardenburg (1932).

Angiomatosis retinae (Lindau's disease) is a rare condition discovered by von Hippel in 1904. The retinal vessels give way in connection with angioma formation in the retina, producing subretinal hemorrhage. Treacher Collins had found it in a man and his sister. It was later observed in two sisters, in two brothers, in a brother and sister, in two brothers. Lindau (1930) finds this form of retinal tumor to be familial in 20 per cent of cases. Iles (1939) recorded seven cases in one sibship.

Collier (1931) described four sisters: (1) had capillary angioma of the cerebellum with hypernephroma of the kidney, (2) had capillary angioma of the medulla and hypernephroma, (3) had Friedreich's ataxia, (4) had migraine. There were no eye tumors, but two had brain tumors. Usher (1935b) found 119 cases of angiomatosis retinae in the literature, but few were familial. Eight pedigrees contain two or more cases and in five others there was *cerebellar tumor*, which he regards as an alternative manifestation. An essential feature of angiomatosis retinae is growth of the capillaries in the medulla. The method of inheritance is still uncertain but appears to be recessive in some families and irregular dominant in others. Vogt and Meyer (1937) give two pedigrees in which it is irregularly dominant. Cases may remain stationary or improve occasionally. Brain, Greenfield and Northfield (1943) describe a family having Lindau's disease without a cerebellar tumor. There were 5 cases (4♂ 1♀) in four generations, an irregular dominant with two skips. The female case had hemangioblastoma in both retinae and in the spinal cord, as well as other abnormalities. *Retinitis exsudativa* of Coats is a related condition, according to Junius (1934), both being parts of a status varicosus.

Retinitis circinata is a rare form of retinal inflammation in which brilliant white spots are found in a wreath-like pattern around the macula. It is almost confined to old women of sixty to eighty-two. Pollnow (1933), however, cites a case at thirty-eight and another at twenty years. He described the condition in two aged sisters. The inheritance appears to be recessive.

The diseases of Bourneville, Recklinghausen and Hippel-Lindau are three related congenital hereditary syndromes. Their main symptom is spots (naevi), tumefactions and cysts with other congenital malformations in various parts of the body, especially the nervous system. Bourneville's tuberose sclerosis of the brain shows tumors of the retina and optic disc. Similar tumors occur in connection with Recklinghausen's neurofibromatosis. Von Hippel-Lindau disease is angiomatosis retinae et cerebelli. Van der Hoeve (1932) puts the three together as *phakomatoses* or tumor formations, since all may show tumors in the retina and Recklinghausen's disease may also show very small ones in the retina. A fourth, the Sturge-Weber syndrome, is added by Brouwer, Hoeve and Mahoney (1937). Besides naevi and retinal tumors this has telangiectases, buphthalmos and especially calcification in the cerebrum. A girl of twenty with a small retinal tumor had five sibs with Bourneville disease. She married and had six children, three with tumors in the retina and one with epileptic fits. For glioma retinae see Chap. XXVI on cancer.

Retinitis pigmentosa

This retinal disease is also inherited in dominant, recessive or recessive sex-linked pedigrees. The name was first used by Donders in 1857, the disease being discovered when observations of the fundus began after the invention of the ophthalmoscope in the middle of the nineteenth century. Degeneration begins near the equator of the eye, with deposits of pigment in the retina in spidery figures often anterior to blood vessels. According to Levy-Wolff (1940) the body temperature is also lowered, but Dax (1940) and others have found hyperthermia present in several cases. Levy-Wolff also finds cholesterinemia present, which affects the walls of the intra-ocular blood vessels before changes occur in the retinal vessels. "Bone corpuscles" are formed as a part of this malignant sclerotic vascular process, which is restricted to the brain and sense organs and which he believes to be centrally actuated in the hypothalamus. Retinitis pigmentosa is a developmental defect, usually accompanied by night-blindness. The most elaborate study is that of Julia Bell (1922).

Nettleship (1909) included as allied conditions retinitis pigmentosa sine pigmento (described by Leber in 1871), retinitis punctata albescens, gyrate atrophy of the choroid and retina, choroideremia and two types of congenital stationary night-blindness. Retinitis pigmentosa is characterised by its progressive nature, leading to blindness, and by its contracted vision, causing the patient to peer around. Its onset is usually before twenty, and it may even be congenital. Pigment is deposited along the blood vessels, and blindness frequently supervenes before forty. In certain pedigrees it is congenital, in others invariably late, still others show a very rapid course. It is uncertain whether the progressive degeneration leading to blindness arises in the layer of the choroid which is responsible for nutrition of the retina, in the rod and cone layer of the retina itself, or in the retinal blood vessels along which pigment develops.

Many pedigrees of retinitis pigmentosa are free from other defects. Dr. Bell states that out of a total of 919 individuals, 656 taken from 329 sibships have no other defect noted. In 96 cases it was associated with deafness or deaf-mutism. These may be aspects of a common cause, or the association may be due to separate linked factors. A similar relation between retinitis and glaucoma is suggested by the occurrence of eleven cases of glaucoma with retinitis pigmentosa and two cases of glaucoma alone in siblings.

The Laurence-Moon-Biedl syndrome, in which retinitis pigmentosa, polydactyly and hypogenitalism are present, is discussed in Chap. XVIII, on syndromes.

Snell's (1903) valuable pedigree (Fig. 76) shows 29 cases (13♂ 16♀) in five generations, the sibships 27 affected : 17 normal (not a statistically significant departure from equality). Haldane (1938) has given reasons for thinking that this may be a case of partial sex-linkage. This is discussed in the chapter on linkage (p. 76). In Holland, von Wibaut (1931) assumed that there were several recessive forms of retinitis pigmentosa, each with a separate gene, the condition being usually recessive when associated abnormalities are present; but in two-thirds of the cases there are no associated abnormalities. Nettleship found that 4 per cent of the deaf or deaf-mutes had retinitis pigmentosa. Panse (1937) believes that the pathological gene comes into action in the rudimentary diencephalon at a very early stage of development. Dax (1940) investigated eleven cases, tracing 385 relatives in ten pedigrees. Nearly all were single cases, all apparently recessive. All had gray or blue-gray iris, except one with heterochromia iridis. The associated abnormalities are discussed and the conditions interpreted in terms of varying degrees of degeneration of the nervous system.

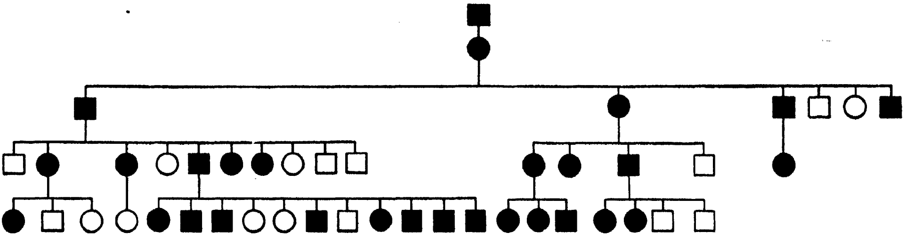

Fig. 76. Dominant pedigree of retinitis pigmentosa, probably showing partial sex-linkage. (After Snell)

Wibaut recognized nine different forms of retinitis pigmentosa. He found 26 pedigrees dominant, with 148 ♂ and 149 ♀ affected. The recessive pedigrees were 264 with 317 ♂ and 235 ♀ affected. As no marriage between recessives has been recorded, it is uncertain how many different recessive genes may exist. In many families it is uncertain whether the condition is recessive or partially dominant. In recessive pedigrees there is an excess of affected males (57·5 per cent). Deafness is present in 22 per cent of the pedigrees and defects of the nervous system in 6 per cent. These may represent different genes.

Usher (1930) published two important pedigrees. Pedigree I (in Glasgow) contained 243 members in six generations. In this pedigree, night-blindness, which is congenital or develops in childhood, is an early stage of retinitis pigmentosa which appears gradually in middle life and seldom produces total blindness even in old age. The affected were 20 ♂ 17 ♀, sibships 35 affected : 47 normal. The excess of normals is probably due to a higher death-rate of the affected. The inheritance is strictly dominant with no skip. Absence of sex-linkage is indicated by transmission to grandchild of same sex, 16 : opposite sex, 20. Pedigree II, also from Scotland, is an extension of Hine's case. It now shows seven generations with 18 cases (10♂ 8♀) in the first five generations, the sibships numbering 17 affected : 32 normal. The inheritance is dominant but shows four skips, in one case for two successive generations. Otosclerosis was present in one branch of the family, with fourteen cases in three generations, four of them having retinitis pigmentosa as well. This pedigree dates from a man born in E. Lothian in 1734. The onset of night-blindness is late and several end in blindness. Usher suggests that otosclerosis may be a substitute or equivalent of retinitis pigmentosa in this family, but this is unlikely as four persons have both and they are independently inherited in other families.

McQuarrie (1935) collected in Liverpool two extensive pedigrees of hereditary blindness. One has been variously diagnosed as optic atrophy, retinitis pigmentosa and degeneration of the macula. There were 36 cases (19♂ 17♀) in four generations, the sibships 35 affected: 25 normal, inheritance strictly dominant. Pigmentation of the macula, beginning under ten years of age, was followed by its atrophy and in many the optic nerve atrophied as well. There was no night-blindness nor mental defect, but the cases ended in blindness, some showing pigmentation of the retina. The other family shows ordinary retinitis pigmentosa, 21 cases in five generations numbering 152 persons. The onset varies from twelve to twenty-five years, and there are no associated defects. It is recessive sex-linked except for one heterozygous female who died blind, but the cause was unknown. She may have been a case of varying dominance.

Scheurlen (1935) reviewed the 506 cases (325♂ 181♀) of retinitis pigmentosa seen in the Tübingen eye clinic since 1877. He recognizes infantile, juvenile and later-age forms not producing complete blindness. The form *sine pigmento* was found in children and young persons only, an early stage of the juvenile form. Of *retinitis punctata albescens* there were only 9 cases. Of 29 published pedigrees, 27 were recessive (see Fig. 77) and only 2 dominant. The 56 sibships treated statistically indicate that a single recessive gene is present. In one recessive pedigree there were affected members in generations I, VI, VIII, IX and X, always from normal parents; in another, generations II, VII, IX and XI showed cases. Of 94 probands, 72 had no children. Neame (1945) records the condition in two sisters and a brother. The fundi were albinotic, with a stippled appearance, and two of them were night-blind. The normal parents were first cousins. In comment, Mr. O. G. Morgan recorded the same condition in three sisters, two of whom were night-blind. The parents were normal and unrelated, but the mother had an affected brother. Scheurlen concluded that the frequency of retinitis pigmentosa in the population has not changed in the last fifty years and that the recessive gene is uniformly distributed in the population. Obviously those transmitting this very serious defect should not have children, but owing to the frequently late onset of symptoms the damage is often done before it is known that the parents are carrying the gene.

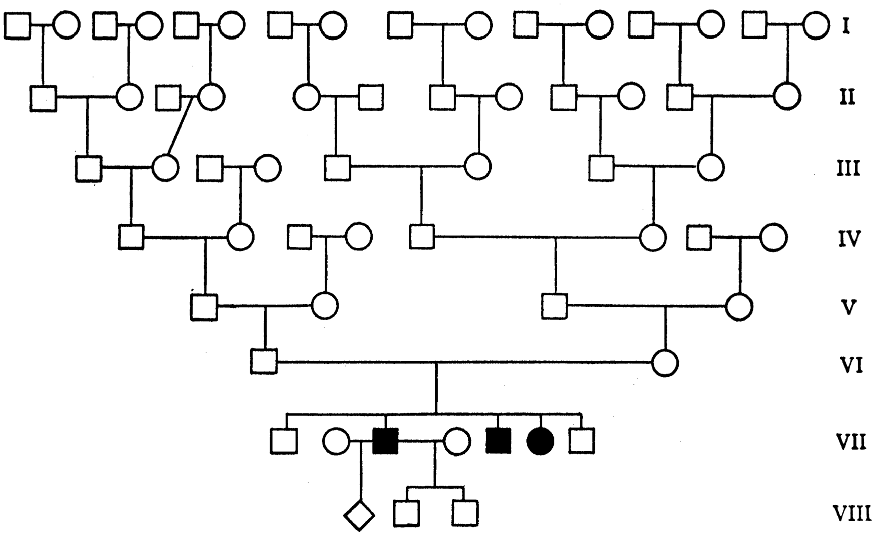

Fig. 77. Recessive pedigree of retinitis pigmentosa. (After Scheurlen)

Allan (1937) finds that when the gene is dominant those affected are only half-blind, night-blind or "moon-eyed," the age of onset being twenty-five to forty years and rarely progressing to blindness even after sixty. When a sex-linked recessive, the age of onset is in the second or third decade and complete blindness supervenes at forty to fifty. When simple recessive the sight begins to fail in the first decade and the child is stone blind before twenty. He finds the same law to hold regarding peroneal atrophy. The explanation, as he points out, lies in the fact that in the dominant form the affected individual is heterozygous, one defective gene being pitted against its normal allele. In the sex-linked form this gene is paired against the Y-chromosome (generally without the corresponding normal gene); while in the recessive form two defective genes are reinforcing each other and so produce a more severe condition. Allan cites nine pedigrees of retinitis pigmentosa, two of them dominant, six recessive and one sex-linked. A dominant pedigree has 20 cases (10♂ 10♀) in six generations. There are difficulties in any attempt to rationalize these relations completely at present. In sex-linked characters such as color-blindness, two doses in the female appear to produce the same effect as one in the male.

A pedigree of Usher (1935b), extended from earlier observations of Nettleship and Bell, contains both retinitis pigmentosa and myopia (Fig. 78). The former is sex-linked, with eleven cases in five generations. All the affected males except one and the five transmitting females had myopia (2–8 diopters). The myopia is thus dominant and linked with the retinal defect in the X-chromosome. Usher found 299 published cases of retinitis pigmentosa (174♂ 125♀). Fifty per cent were also myopic, while among 400 medical students at Aberdeen 19 per cent were myopes and the general population contained 10 to 15 per cent. In Fig. 78, V. 12, 16, who were half-brothers, were totally color blind, their visible spectrum extending only from 670–425 mμ (the red end was shortened). Usher refers to two other sex-linked pedigrees, Seggel's and Frazer's. Klainguti (1923) found four cases of retinitis pigmentosa with total color-blindness in a sibship of seven, the parents related. This means either linkage or a pleiotropic effect. Mere association seems less probable. Usher suggested linkage of the genes for retinitis pigmentosa and color-blindness. They appear to be in different parts of the X-chromosome (see Fig. 23, p. 81).

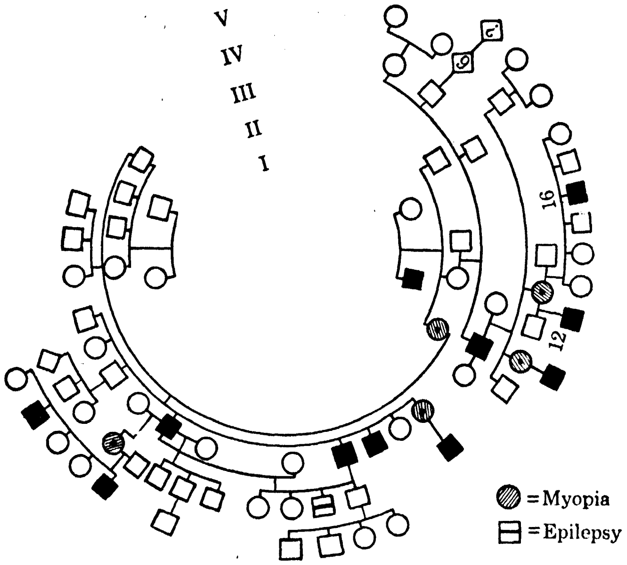

Fig. 78. Recessive sex-linked retinitis pigmentosa and dominant sex-linked myopia. (After Nettleship, Bell & Usher)

Fraser Roberts (1940) pooled the dominant pedigrees of retinitis pigmentosa (taken from Haldane, 1936) and found the following results:

	Affected	*Unaffected*
Offspring of same sex as affected paternal grandparent	81	60
Offspring of opposite sex to affected paternal grandparent	64	83

Thus there were 164 non-cross-overs to 124 cross-overs. The chance of this deviation from equality is only 1 in 106, so there is good evidence of partial sex-linkage. It was found that only 40 per cent of the families showed sex-linkage, the cross-over value being about 28 per cent. In the other families the gene was autosomal.

Mann (1928) described a family in which ten members in the third generation, belonging to three families of cousins, had retinitis pigmentosa and two others had Leber's disease. The parents and grandparents were normal, the inheritance recessive for both diseases. Allan and Herndon (1944) describe a family with 89 cases of dominant retinitis pigmentosa. An affected man married a normal woman belonging to a family which produced 22 male idiots in five generations. The idiocy was recessive sex-linked. The above marriage produced three sons who were all idiots, one having also retinitis pigmentosa. There were three normal daughters and seven stillbirths or deaths in infancy.

Biró (1944) finds that the recessive form of pigmentary degeneration of the retina is frequently connected with disturbances of hearing. Both develop together. He regards atrophy of the organ of Corti and the acoustic nerve as corresponding with retinal degeneration and optic nerve atrophy.

Leber's Disease or Optic Atrophy

Atrophy may arise in the optic nerve or result from a lesion of the retina. Part of the fibres in this nerve continue from the optic disc or papille through the retina to the macula lutea. This is the region of sharpest vision, and a central scotoma in this area (resulting from atrophy of the nerve) produces semi-blindness, while the peripheral field may remain functional. Idiopathic or hereditary optic atrophy is usually of the type described by Leber (1871). In this paper he reported 16 cases in four families.

Leber's disease, like several other ocular defects, occurs in dominant, recessive and sex-linked forms, but many pedigrees do not fit consistently any of these types of heredity and require some special explanation. The inheritance of Leber's disease remains one of the most puzzling problems in human genetics. Probably the pedigrees of over a thousand families have been published. The bulk of them appear to show sex-linkage, and simple dominant or recessive pedigrees are rare. The large pedigree of Waardenburg (Fig. 79) with 18 cases (16 ♂ 2 ♀) in four generations is sex-linked, but the condition is partly dominant, since two heterozygous females are affected. This shows that, as with ordinary dominant and recessive, the line between sex-linked dominant and sex-linked recessive is not a sharp one.

Waardenburg (1932) has a clear case of recessive congenital optic atrophy and another recessive family (Behr type) in which it is combined with nystagmus and defects of the nervous system. This is probably a different gene. Gunn described recessive infantile atrophy in mother, son and daughter resulting from a cousin marriage. In Griscom's (1921) dominant family, with 14 cases (8♂ 6♀) in three generations the condition was congenital or infantile, was always inherited through the father and showed one skip. Relatively little attention has been paid to the disease in America, but Merritt (1930) described a Swiss family with 4 cases (all ♂) in two generations.

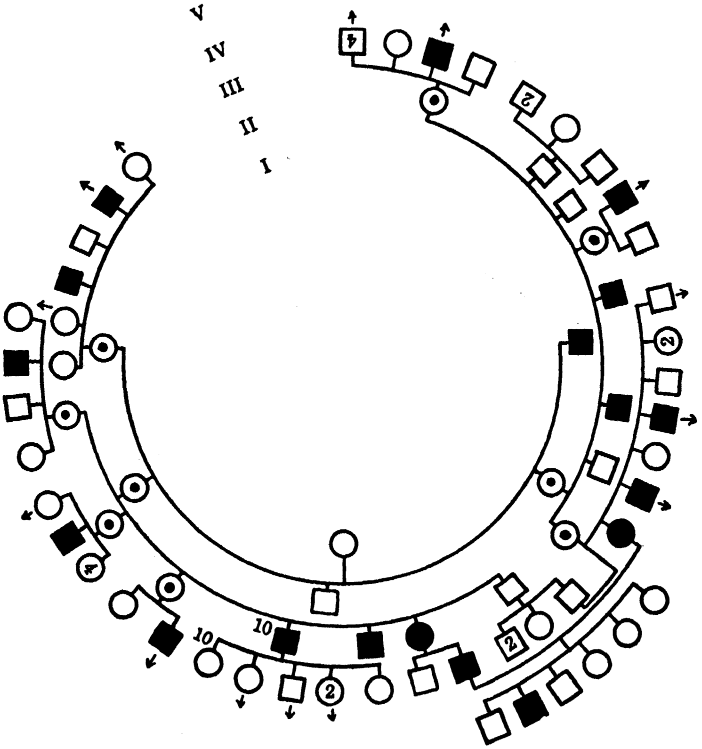

Fig. 79. Recessive sex-linked optic atrophy. (After Waardenburg)

Hogben (1932) concluded on statistical grounds that there are two forms of Leber's disease, most European families being recessive sex-linked while in the majority of Japanese families two dominant autosomal genes may be involved. A bigenic hypothesis would explain the large excess of normals in such pedigrees as Yô's Chinese family (Fig. 2, p. 8) in Komai (1934); but it would not explain the large excess of affected males. Cases of bigenic inheritance are rarer than was formerly supposed. Lack of penetrance is the more likely explanation of the excess of normals.

Nettleship (1909) found that Leber's disease could occur in women. He also found that two normal parents may have an affected daughter and that an abnormal daughter may have normal sons. In the Nettleship pedigrees, 12 families from affected ♀ × normal ♂ gave 64 children, 31 normal: 33 affected (1 : 1), and of the latter there were 21♂ and 12♀. Transmitter ♀ × normal ♂ gave 215 children, 150 normal: 65 affected.

Macklin (1927e) cites a pedigree of Worton in which he claims that the transmission is not according to the "law of Nasse" (see Chap. XIV) but according to that of Lossen, i.e., that affected men cannot transmit. In this pedigree of optic atrophy, only three affected men have children. Eight of the latter are girls, but none of them had yet had children. Many of the pedigrees which are supposed to show inability of the male to transmit are subject to the criticism that males have not survived or not married.

A typical pedigree of Leber's disease, showing sex-linkage, confined to males and transmitted by females, is seen in Fig. 80, taken from Vogt (1922). Pines and Tron (1925) cite a case where five brothers in a family of thirteen were afflicted. Their mother's brother was also affected. The onset of the disease began in the uncle at twelve years of age, and in the five brothers at the ages respectively of 28, 20, 14, 31, 31. Schönenberger (1926), in reviewing the subject, brings together 127 pedigrees by 16 authors. Of those affected, 534 are ♂ to 99♀. In some of the pedigrees no female has it, in others they are often affected. None of these pedigrees shows whether a man can transmit through a normal daughter to his grandsons. In one a female is affected as well as her brother. This may be a case of variable dominance.

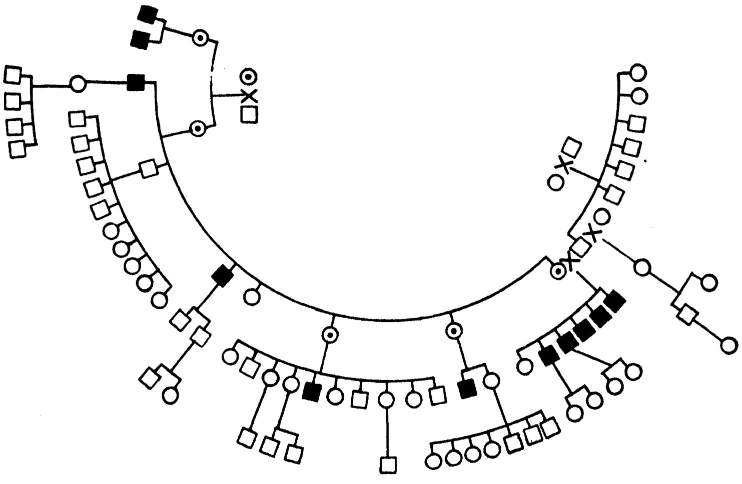

Fig. 80. Pedigree of optic atrophy (Leber's disease). (After Vogt)

Kawakami (1926) also finds the condition following the X-chromosome in his pedigrees, but some heterozygous females showing it. The age of onset of the disease varies, as does also its occurrence in different races, the Japanese exhibiting it most frequently. Usher (1927) describes a family with sixteen cases in six generations, and another with eight cases in five generations. There is said to be no consanguinity of the parents in either pedigree, but in both the inheritance is recessive.

Bell (1928) collected the reports of 904 families, 782 European, 122 Japanese. In the former, 15.5 per cent of the affected are female, in the latter, 40.9 per cent. In Komai's 41 pedigrees of optic atrophy in Japanese, only three show transmission by an affected male — to 2 sons, one son, and 3 sons and a daughter respectively, although they have a total of 39 children (one having 4 sons and 6 daughters). This is an approach to Lossen's supposed law and seems to show that sperms bearing the gene for optic atrophy are less viable. Bell gives graphs for the age of onset in ♂ and ♀ in Europe and Japan. In the Japanese the maximum onset is at about fifteen years, the curves for ♂ and ♀ being very similar, whereas in European women there is one peak at fifteen (puberty) and another at twenty to forty-three, perhaps due to toxic effects of pregnancy. European males show one high peak at *ca.* twenty-four years. Since the onset is so different for European and Japanese females, she suggests that the dominant and sex-linked forms represent different genes. When a European mother is affected, the onset is earlier in her sons (perhaps because a different gene is involved in these families). Recovery sometimes takes place, which may have a connection with the variable dominance. Nevin's (1933) family has 8 cases (7♂ 1♀) in three generations. The inheritance is sex-linked recessive, except that a sister of two affected brothers is also affected.

Komai (1934) regards such pedigrees as Fig. 8, p. 15, as not sex-linked but strictly dominant in the male and exceptionally so in the female. He states that optic atrophy is the commonest eye disease in Japan.

Waardenburg (1935) finds that congenital forms are mainly recessive while the infantile-juvenile type is a simple dominant, as in the Griscom pedigree which he thinks is not typical Leber's disease. He finds that in Japanese pedigrees 41.4 per cent of the women are affected (in Europe 10 to 16.6 per cent) because the condition is partially dominant in Japanese women. He also finds that the prenatal mortality of male foetuses with Leber's disease is less than normal and concludes that they must have a *higher* vitality. The excess of conductor over non-conductor females is similarly explained by selection in favor of the former. In explanation, Waardenburg fell back on a complicated theory of inheritance involving changes in the cytoplasm, which was supported by Imai and Moriwake (1936). They found the frequency of affected females to be 8.4 per cent for the Germans, 20.6 per cent for the French, 21.6 per cent for the English and 70 per cent in Japan, and suggested that these differences could be accounted for by differences in the sensitivity of the cytoplasm to the female sex hormone. Such an hypothesis appears highly improbable.

Hubert (1932) described a form of congenital optic atrophy in which there was no central scotoma. There were 10 cases (8♂ 2♀) in three generations, the inheritance dominant, sibships numbering 10 affected: 14 normal, three cases being diagnosed as retinitis pigmentosa. Bedell (1934) describes a family with 11 cases (8♂ 3♀) in four generations. All cases were inherited through the mother, who was affected in two cases and normal in two. This is perhaps best regarded as sex-linked with irregular dominance in the female.

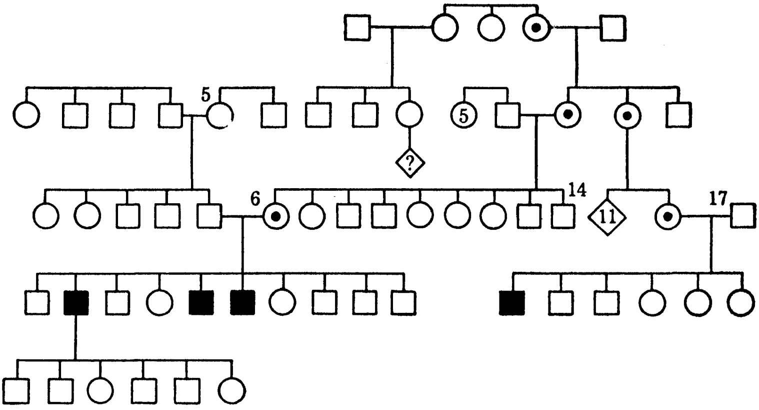

Fig. 81. Orkney family with Leber's optic atrophy. (After Russell)

Figure 81 from Russell (1931, 1932) illustrates well the difficulties in interpreting many pedigrees of Leber's disease. The family lives in the Orkneys. Four cases appeared in generation IV, three of them from a marriage of second cousins, time of onset from twenty to forty years. The sibships number 4 affected : 12 normal, exactly in accord with a simple recessive. But the sex-ratio is 11♂ : 5♀, all the affected are males and III. 16 must have been a carrier. Is it possible that females homozygous for the condition are non-viable? If sex-linked, it would be inherited from I. 4 in both families and should show in some of the males of generation III. Russell suggests that a decrease of vigor in generation IV might account for its appearance, but this is unlikely. On the other hand, if simply recessive it could be transmitted through II. 5 and III. 6.

Halbertsma (1934) has five pedigrees of Leber's disease, four of which are typically sex-linked recessive with a total of 44 affected males. The fifth (Fig. 82), from Leiden, has points of special interest. Like some other pedigrees of this condition, it seems to necessitate a change in dominance in generation III. In the first two generations it was an ordinary sex-linked recessive, while in the last two it is a simple dominant. Crossing-over from X to Y would explain III. 1, but the three affected females necessitate a change in dominance. Siemens' (1925) extensive pedigree is strictly recessive sex-linked except that two heterozygous females exhibit the condition. The whole family contains 18 cases (16♂ 2♀) and the sibships containing affected males number 16♂ affected : 15♂ normal. It would be interesting to know if the daughters of III. 10 transmitted the condition to their sons.

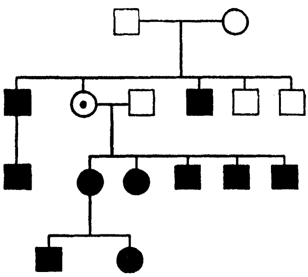

Fig. 82. Dutch family with Leber's optic atrophy. See text. (After Halbertsma)

Stahlin (1931), from a study of many pedigrees, concludes that in addition to Leber's disease there are two other forms of optic atrophy, (1) Behr's optic atrophy of children, (2) a recessive congenital optic atrophy.

Thompson and Cashell's (1935) family (Fig. 83) is a strict dominant, 16 cases (6♂ 10♀) in six generations. It differs from typical Leber's disease in being congenital and stationary with white optic discs and peripheral restriction of sight instead of a central scotoma. There were no other anomalies. The gene may be distinct from that of Leber's disease. The inheritance is entirely through five mothers, but this may be chance.

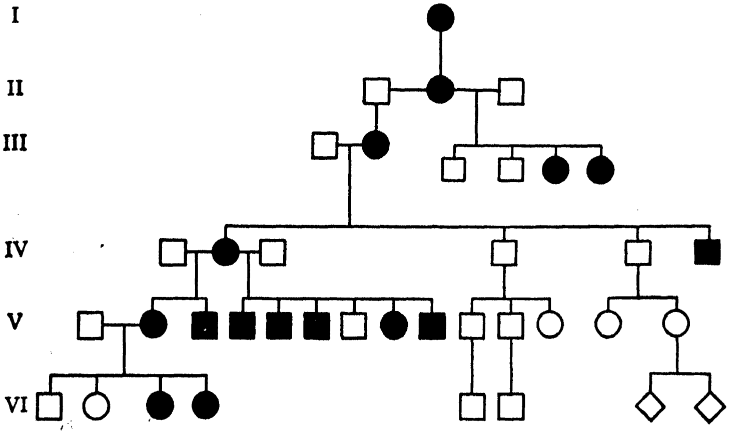

Fig. 83. Dominant pedigree of optic atrophy. (After Thompson & Cashell)

Evidently the problem of variable sex-linkage in Leber's disease will only be solved by further analysis of symptoms, age of onset and other details in many complete pedigrees. It is not yet certain whether a difference in method of inheritance is accompanied by differences in symptoms. The main genetic peculiarity, however, is evidently the variable dominance in the female. The sex-linked form probably most nearly resembles color-blindness in its genetics, but with less frequent transmission by males.

Veit (1940) describes the first family in which sex-linked Leber's disease is associated with recessive deaf-mutism. There were nine cases of Leber's disease, one girl born blind was also an idiot. The four cases of deaf-mutism were in one sibship, the two males having Leber's disease as well and one female transmitting Leber's disease in marriage with another deaf-mute. The two conditions are evidently not linked.

The linkage of Leber's disease with other sex-linked characters is discussed in Chap. IV. Curtius and Decker (1930) published a pedigree with 65 members in four generations, 43 of whom were examined. Of these, 15 had nervous and psychic affections, 10 had *anisocoria* (pupils of unequal diameter) and one had relapsing oculomotor paralysis.

Excavation of the optic disc (end of the optic nerve) is often described. Gut (1937) studied the inheritance in 35 families including 160 persons. In 12 families deep excavation was present in both parents and in 25 of 33 children. From this and other evidence it is concluded that excavation is dominant in inheritance.

Congenital Stationary Night-Blindness (Hemeralopia)[3]

This condition also occurs in dominant, recessive and sex-linked forms. It is attributed to an insufficiency of rods and of retinal purple and generally is unaccompanied by visible changes. The dominant form furnishes one of the largest pedigrees for the inheritance of any human condition, although many other pedigrees now extend to ten or eleven generations. This is the famous pedigree of Jean Nougaret (1637–1719) and his descendants (peasants in the south of France) through ten generations, seven of which were published by Cunier in 1836. Nettleship (1907) worked out the full genealogy to 2116 persons, recognizing the condition as a Mendelian dominant, and the chart of inheritance is given by Bateson (1913) in condensed form. Affected persons are unable to see in a dim light. While strictly dominant, there is an excess of normals in the sibships, in the ratio 134 : 246, partly due to some form of selection, sperm carrying the gene being perhaps less viable, and partly to the fact that all children dying in infancy were considered normal. Rambusch, in Denmark, traced a family through eight generations with 48 affected to 33 normal men and 46 affected to 33 normal women — the reverse of the condition in the French family. In still other families these four categories are equal.

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[3] It has been suggested (*Brit. Med. J.* 1942. ii. 497) that the unsatisfactory terms hemeralopia and nyctalopia be replaced, preferably by nyctamaurosis.

Nettleship (1912) described a family with sex-linked night-blindness associated with myopia, 21 cases (20♂ 1♀) in five generations. In another family studied by Newman (1913), night-blindness is also sex-linked. This family is from Texas, having originated in North Carolina. There is "apparent non-inheritance of the capacity to transmit night-blindness on the part of the sisters of night-blind men." In F_3 and F_5, if there were no consanguineous marriages, there should be equal numbers of females carrying or not carrying night-blindness. But none of the five married sisters of F_3 night-blind men show any trace of night-blindness in their progeny. Newman suggests that possibly night-blindness cannot be inherited through two successive generations in the female line, owing to prolonged association of the defective X-chromosome with a normal X. But other genes can be transmitted through several generations of females without being lost or affected.

In its main essentials the character in this family behaves as a recessive located in the X-chromosome, but, as in hemophilia, there is an excess of abnormals. Thus, of the 36 offspring of the night-blind-carrying daughters of night-blind men, there were 22♂, 14♀, and of these 22, 17 were affected and only 5 not. In this family the night-blindness is usually accompanied by myopia, and almost invariably by strabismus, with frequent occurrence also of *pterygium*. It is believed that all these conditions form one complex, and whether all appear may depend on other factors present. Nettleship thinks pterygium is produced by glare and dust. The sex-linked form of hemeralopia is usually associated with myopia, but this was not the case in Newman's pedigree.

Sedan (1885) published two dominant pedigrees of hemeralopia, one family having 10 cases (5♂ 5♀) in three generations, the other 9 cases (4♂ 5♀) in four generations, no skip. In Swanzy's (1873) family the condition was probably dominant. In Morton's (1893) family it is evidently recessive sex-linked, with fifteen cases (all males) in five generations. In the second generation of this pedigree a normal son is supposed to transmit the condition to two grandsons. Probably this was a daughter instead of a son. In this pedigree every one of the eight recorded females is a transmitter. In another sex-linked pedigree (Cutler, 1895) there were six cases (males) in four generations, and the four surviving females were again all carriers. Ammann's (1898) family had twelve cases (all males) in five generations, the inheritance strictly sex-linked. All the affected were also high-grade myopic, and seven normal females transmitted. A large pedigree of hemeralopia with myopia and astigmatism, by Kleiner (1923), is an extension of Pflüger's pedigree in 1881. Strictly sex-linked, it includes 17 affected males in three generations.

Bell (1922) states that the inheritance of night-blindness was recognized as early as 1774 and gives a number of pedigrees. She found that 86 per cent of daughters transmitted. In a recessive sex-linked character all daughters of affected males may be expected to transmit to half their sons, because all have received the defective X-chromosome from their father. In small families, however, it may happen that only normal sons appear even when the mother is heterozygous for the condition.

Extensive pedigrees of night-blindness (hemeralopia) running into five, six, or even eight generations were published by Varelmann (1925), with many clinical details. He also found it to be a recessive sex-linked character. When the father was affected and the mother normal, 38 of the sons were normal and 4 affected (the latter because their mother was a transmitter); of 23 daughters, 21 were shown to be carriers. (Only half the daughters of a carrier mother will be carriers.) Of the 154 sons from normal fathers and carrier mothers, 53 were normal, 93 affected; hence a large excess of abnormal sons.

A recent pedigree (Riddell, 1940) has eight night-blind males in three generations. They frequently show myopic astigmatism and a squint, with defective sensitivity for yellow-blue. The condition is quite likely allelic to color-blindness. With the reduced lighting in wartime, night-blindness is a serious disability. Temporary night-blindness, as a non-inherited condition, may be due to lack of vitamin A or associated with nerve exhaustion, malaria, rheumatism or other causes. The prescription of liver for night-blindness was common in the Middle Ages, and is recorded on an Egyptian papyrus, 1500 B.C. Hind (1863) cited many cases of temporary night-blindness in Labrador, but he says (p. 163) "they always recover their sight as soon as they reach the settlements and get a change of diet."

Recessive night-blindness has been reported several times. Gassler (1925) described a consanguineous family of Vogt with recessive hemeralopia and myopia. Four cousin marriages produced 9 cases (3 ♂ 6 ♀) in a total of 41 sibs. Oguchi (1907) reported recessive hemeralopia without myopia in a family with much inbreeding in Japan.

This is evidently a distinct gene, as the fundus has the peculiar appearance of "partially stripped gilt," which disappears after two hours in darkness and probably depends on the rods in the retina. It may be related to retinitis punctata albescens. Oguchi (1926) thinks it is due to two abnormalities in the retina, (1) anomalous division of the cones, (2) formation of an intermediate layer. Many small pedigrees of *Oguchi's disease* have been published in Japan (Komai, 1934) and it has since been recorded as a rarity in Europe. Kawakami (1925) found night-blindness common in Japan, occurring as dominant, recessive or sex-linked. He recorded 20 families while Oguchi (1926) described a sibship having three cases of hemeralopia, three of Oguchi's disease and two normal sibs. Another family had two cases with six normal sibs. Endelman (1931) found a brother and sister with Oguchi's disease, from a consanguineous marriage in Poland. They are stated to have belonged to the Armenoid race, with convex nose, shovel-incisors and a marked zygomatic arch, which was regarded as evidence that they were of Mongolian descent. Scheerer described the first European case in 1927.

Night-blindness, or "moon eye," has been described in a herd of shorthorn cattle in Oklahoma (Craft, 1927). They are normal by day, but are so blind at night that they stumble over slight obstacles. They were descended through inbreeding from a common ancestor, and as normal parents gave some night-blind calves, the condition is apparently recessive.

Rodless retina is a condition accidentally discovered in albino mice and not known to occur in human beings. The retina of both eyes differs from the normal in the complete absence of the light-sensitive (rod) layer and great reduction in the number of rows of nuclei in the external nuclear layer. (Cones are normally absent in the mouse.) Keeler (1927, 1928) found that this condition is a simple recessive. There is no visible lesion of the eye but it causes complete blindness, and it can only be discovered from sections, because blind mice behave exactly like mice with normal vision. Three conditions of the retina were found, in which the external nuclear layer consisted of 1, 3, or 6 rows of nuclei, whereas in the normal retina this layer contains 15 rows. The 3-row and 6-row conditions appear to be modifications of the 1-row, perhaps due to a genetic modifying factor.

Glaucoma is a disease of the eye with intense intra-ocular pressure due to blocking of the lymph drainage canal, whether congenitally or by infection, resulting in hardness of the eye, atrophy of the retina and ultimate blindness. It is relatively rare and is probably generally inherited. James (1927) gives a dominant pedigree with eight cases in two generations. Some pedigrees also show "anticipation." Kamenetzki (1925) described a juvenile form of glaucoma, which usually manifests itself at puberty and was confined to males, while in other forms of glaucoma more women than men are usually affected. The pedigree of Kamenetzki (Fig. 84), from the Russian farming population around Irkutsk, also shows recessive sex-linked inheritance. The case of transmission from an affected man through his daughter to a grandson is regarded as doubtful, though there is no reason why it should not occur.

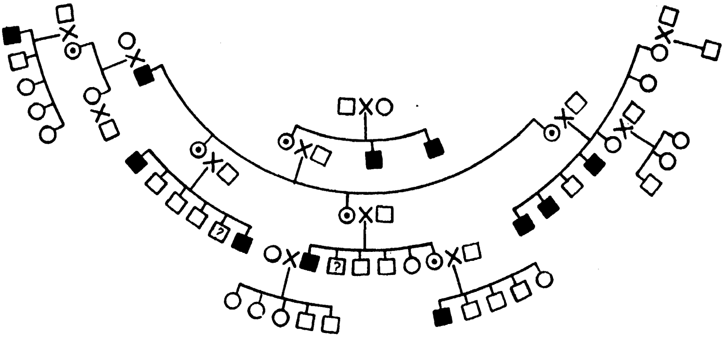

Fig. 84. Recessive sex-linked inheritance of juvenile glaucoma. (After Kamenetzki)

Courtney and Hill (1931) have a pedigree of *dominant juvenile glaucoma simplex*. A Scottish family settled in Virginia has 18 cases (10♂ 8♀) in five generations, with two cases of failure of penetrance in the third generation. The onset is usually in the second or third decade and the disease runs a rapid course, necessitating iridectomy. The glaucomatous eye usually has a small cornea, but in this family the cornea is of normal size and there are no associated ocular defects. Many authors mention a predisposition of dark eyes to glaucoma. This might have either a genetical or a physiological basis.

Another dominant pedigree (Zorab, 1932) contains 7 cases (6♂ 1♀) in three generations without loss of vision. Mr. Humphrey Neame reported at the same time a family with 9 cases (4♂ 5♀) in three generations. Five previous dominant pedigrees also show an excess of affected males, the total affected being 25♂ : 10♀. A German pedigree of adult glaucoma (Wolfsohn-Jaffé, 1935) has 9 cases (6♂ 3♀) in three generations.

That anticipation may be a reality in glaucoma is indicated by de Grósz (*Brit. Med. J.* 1939, i. 891), who cites a case of a man afflicted at eighty-three, his daughter at sixty-two, her two sons at forty-four and thirty-eight. In another case, man and wife developed glaucoma at fifty-four and fifty-seven. Of the five children, it appeared in two daughters at thirty-eight and thirty-five, and in a grandson at twenty. It is stated to be prevalent in Hungarian Jews.

Hydrophthalmus or dropsy of the eye is similar to glaucoma in symptoms but occurs in children. According to Waardenburg (1932), congenital hereditary hydrophthalmus is a simple recessive but the published cases give a ratio of 5♂ : 3♀ afflicted, the reason for which is not known. It is also recessive in rabbits, and it occurs in dogs and calves.

Sorsby (1935) points out the association of certain ocular defects with skeletal changes. Syndactyly with aniridia is said to be widely known although no cases published. Brachydactyly with microcornea is recorded in father and son. Apical dystrophy of hands and feet with bilateral macular coloboma was observed in a mother and five of seven children. These suggest genetic linkage, though they might be the effects of a single gene. Lobster-hand and aniridia (Savin and Sorsby, 1935) may be only a chance association. Arachnodactyly with ectopia lentis and the Laurence-Moon-Biedl syndrome will be considered under syndromes.

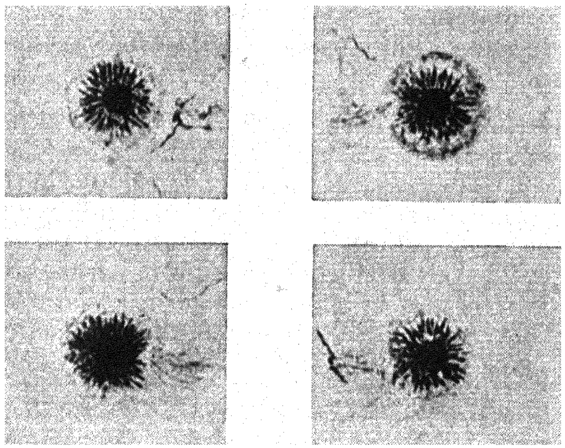

Fig. 85. Eyes of a pair of MZ female twins aged 80, showing pingueculae (a triangular yellowish spot on one side of iris) in the four eyes. (After Vogt)

This chapter may profitably end with some detailed observations of Vogt (1938) on the senile ocular changes in aged identical twins. He shows that senile eye characters appear in both members of a pair in nearly identical form and that they are determined in the germplasm. The wrinkling of the skin and face, the pattern of hair-loss and graying and the time of graying is the same. Twenty-three pairs of aged twins were studied, fifteen of them monozygotic. A pair of MZ female twins aged eighty show almost identical *pingueculae* (Fig. 85) (a triangular yellowish patch in the cornea on both sides of the iris) with *Krukenberg's pigment spindle* (a vertical spindle-shaped brownish-red opacity on the posterior surface of the cornea) and the same type of senile cataract in all four eyes. Vogt gives a pedigree showing the inheritance of Krukenberg's spindle. Both twins were slightly myopic, and all four eyes also had *cornea guttata senilis* (spotted cornea due to dystrophy of the endothelial cells). They also, at eighty, developed simultaneously retinitis hemorrhagica. In nine other pairs, aged fifty-five to eighty-one, the pingueculae were weak, in fourteen pairs strong or very strong, the identical pairs being alike in these particulars, so it is evident that the presence or absence of senile pingueculae is inherited. Vogt *et al.* (1939) give a fuller and highly documented account of the eye characters of aged twins, which is unique. Thomson and Ballantyne (1927) give an earlier account of Krukenberg's spindle, with a colored plate.

Pterygium is frequently supposed to be produced by "wind and weather" but only 1 in 1000 has it. A patch of thickened conjunctiva generally runs from the iris to a broader base at the inner canthus. Two pairs of female identical twins, aged fifty-five and seventy-five respectively, had pterygium in all their eyes. Vogt finds it is probably not dominant. *Unilateral gerontoxon* (equatorial displacement of a lens in the aged) is known to be inherited in successive generations. The *arcus senilis* of gerontoxon was present in both eyes in a pair of male twins fifty-four years of age. It is probably dominant in inheritance.

A pair of male twins sixty-seven years of age showed congenital heterochromia iridis. Both right eyes were blue with pigment naevi (Fig. 29, p. 112) and a *dark brown border around the pupil.* This border or edge is microscopical and the slit lamp is necessary to bring out the detail (see p. 188). It is only $\frac{1}{8}$ mm. in width and brownish in color. The two left eyes of this pair were brown, with a dark brown ring around the pupil in the sphincter region (Fig. 29, right) and no border to the pupil. They were also both drinkers and apoplectics. That this pupillar border composed of lobes like granules, is inherited is shown by a pair of female twins in which it is present in all four eyes. Even its structure, variations and senile changes are inherited. In a pair of twins sixty-eight years old the dark granules of which it is composed have disappeared, leaving a smooth edge except at certain points. It may also be lost by radial splitting or become transparent or the pigment granules may be scattered in the iris or wander into the iris mesoderm. The destruction of this border usually begins at fifty-five. The time and manner of its disappearance is shown by twin studies to be inherited.

The zonula of Zinn or suspensory ligament of the lens may be weak, causing congenital displacement of the lens, or a gene may produce the displacement between the ages of twenty-five and seventy. Vogt also shows senile destruction of the vitreous in a pair of male twins aged seventy-four, as well as partial atrophy of the choroid membrane. Granules in the end of the optic nerve were seen in all four eyes of another pair of identical male twins with tower skull.

In a detailed study of sixteen pairs of identical twins (MZ) and seven pairs of fraternal twins (DZ), Huber (1931) confirms the results of Waardenburg and others. He found the range of difference in corneal refraction to be only 0–1.5 diopters in MZ, for corneal astigmatism, .5 diopter, for total refraction 1.5 diopters. The sharpness of vision, color of iris, distribution of iris pigment, pupillary rim, the structure of the glands of Krause, remains of the pupillar membrane, eyelids, eyebrows, congenital lens opacity; form, color and excavation of the optic disc; the fundus, as well as the form and position of the teeth showed the greatest similarity in MZ and are therefore hereditary. The DZ showed marked differences.

Loeffler (1932) described an eye defect mutation in the white mouse which is of interest in relation to human genetics. The condition is an autosomal recessive. The young are born with their eyes open. The lids bleed, forming an exudate which covers the eye but disappears in five to six days, leaving a median circular white mark on the cornea. The eye-opening is small and the cornea later shows turbidity. The condition varies from nearly normal to one of phthisis bulbi in which the eye degenerates completely. The manifestation of the gene is influenced by a number of inhibiting and promoting factors which are regarded as pleiotropic effects of the normal genes. There is at least one inhibitor in the sex chromosome, and a close relation is shown to the reactions produced by various genes in the genotype.

Huber (1943) discusses and disproves the theory that senile diseases of the eye are due to a process of wearing out. He shows in the case of senile cataract, retinitis pigmentosa and senile macular degeneration that these are homochronous hereditary diseases, other influences being secondary in that they may serve to hasten or precipitate the condition. He concludes that senile cataract and senile macular degeneration are purely genotypically determined age changes in the eye.

LITERATURE

Adie, W. J. 1931. Pseudo-Argyll Robertson pupils with absent tendon reflexes. *Brit. Med. J.* i. 928–930.

Aichel, O. 1932. Epicanthus, Mongolenfalte, Negerfalte, Hottentottenfalte, Indianerfalte. *Zeits. f. Morph. u. Anthrop.* 31:123–166. Pls. 5.

Allan, W. 1937. Eugenic significance of retinitis pigmentosa. *Arch. of Ophth.* 18:938–947.

Allan, W. & Herndon, C. N. 1944. Retinitis pigmentosa and apparently sex-linked idiocy. *J. Hered.* 35:40–43.

Allen, M. 1942. Primary hereditary nystagmus. *J. Hered.* 33:454–456.

Ammann, E. 1898. Das Vererbungsgesetz der Hämophilie bei der Nachtblindheit. *Correspzbl. f. Schweiz. Ärzte* 28:623–626.

von Ammon, F. A. 1831. Der Epicanthus. *Zeits. f. Ophthalmol.* P. 535.

Armaignac, H. 1914. Curieux cas de ptérygion familial héréditaire. *Ann. d'Oc.* 151:469.

Ash, W. M. 1922. Hereditary microphthalmia. *Brit. Med. Journ.* i. 558–559.

Attenborough, V. M. 1945. Three sisters with familial corneal dystrophy. *Proc. Roy. Soc. Med.* 38:37.

Barbosa Sueiro, M. B. 1931. Sur la transmission héréditaires de "l'epicanthus lateralis." *Arquivo Anat. e Antrop.* 13:583–594. Figs. 8.

Barrington, Amy & Pearson, K. 1909. A first study of the inheritance of vision and of the relative influence of heredity and environment on sight. *Eugen. Lab. Mem.* V. Pp. 61.

Bateson, W. 1913. *Mendel's Principles of Heredity.* Cambridge Press. Pp. 413.

Batten, F. E. 1903. Cerebral degeneration with symmetrical changes in the maculae in two members of a family. *Trans. Ophth. Soc. U. K.* 23:386–390.

Bedell, A. J. 1934. Hereditary optic atrophy (Leber's disease). *Amer. J. Ophth.* 17:195–205. Figs. 5.

Bell, Julia. 1922. Retinitis pigmentosa and allied diseases, congenital stationary night-blindness, glioma retinae. *Treas. Human Inher.* 2. Pp. 123. Pls. 26.

———. 1928. The age of onset in hereditary optic atrophy. *Ann. of Eugen.* 3:269–276.

———. 1931. Hereditary optic atrophy (Leber's disease). *Eugenics Lab. Memoirs* XXVI. London. Pp. 99, pls. 16.

———. 1932. On some hereditary structural anomalies of the eye and on the inheritance of glaucoma. *Treas. Hum. Inher.* Vol. II, Pt. V, 425–555. Pls. 37.

*Berry, G. A. 1888. *Ophth. Hosp. Repts.* 12:255.

Billings, M. L. 1942. Nystagmus through four generations. *J. Hered.* 33:457.

Bingel, A. 1937. Braune Augenlider, ein Rassezeichen? *Münch. Med. Wochens.* 84:1531–1532. Figs. 2.

Biró, I. 1934. Vererbung von Ptosis und Epicanthus in drei Generationen. *Zeits. f. Augenhlk.* 84:106.

———. 1944. Ueber den Zusammenhang von Degeneratio pigmentosa retinae und Störungen des Gehörs. *Ophthalmologica* 107:149–157.

Blatt, N. 1924. Distichiasis congenita vera. *Zeits. f. Augenhlk.* 53:325–338. Figs. 6.

———. 1924a. Die Vererbung der Anisometropie. *Arch. f. Ophth.* 114:604–635. Figs. 9.

Blue, R. 1919. Family degeneration of the macula lutea. *J. Am. Med. Assn.* 73:1328–1331.

Bolk, L. 1929. Origin of racial characteristics in man. *Am. J. Phys. Anthrop.* 13:1–28.

Bourne, M. C., Campbell, D. R. & Tansley, K. 1938. Hereditary form of retinal degeneration in the rat, associated with cataract. *Proc. Roy. Soc. Med.* 31:945–946.

———. 1938. Hereditary degeneration of the rat retina. *Brit. J. Ophthal.* 22:613–623.

Bourne, M. C. & Grüneberg, H. 1939. Degeneration of the rat retina and cataract, a new recessive gene in the rat (*Rattus norvegicus*). *J. Hered.* 30:131–136. Figs. 5.

Bradburne, A. A. 1912. Hereditary ophthalmoplegia in five generations. *Trans. Ophth. Soc. U. K.* 32:142–153.

Brailey, A. R. 1906. Congenital distichiasis. *Trans. Ophth. Soc. U. K.* 26:16–22.

Brailey, W. A. 1890. Double microphthalmos with defective development of iris, teeth and anus. *Trans. Ophth. Soc. U. K.* 10:139–140.

Brain, W. R. 1938. Exophthalmic ophthalmoplegia. *Quart. J. Med.* 31:293–323. Pls. 3.

Brain, W. R., Greenfield, J. G. & Northfield, D. W. C. 1943. A case of atypical Lindau's disease. *J. Neur. & Psychiat.* 6:32–37. Figs. 4.

Braun, W. 1935. Ueber familiäres Vorkommen von Drüsen der Papille. *Klin. Mon. f. Augenhlk.* 94:734–738.

Briggs, H. H. 1918. Hereditary congenital ptosis, with report of sixty-four cases conforming to the Mendelian rule of dominance. *Trans. Amer. Ophth. Soc.* 16:255–276.

———. 1919. *Am. J. Ophth.* 2:408–417.

Brodsky, I. & Waddy, G. 1940. Cryptophthalmos or ablepharia. *Med. J. Australia* 1:894–898. Figs. 5.

Brouwer, B., van der Hoeve, J. & Mahoney, W. 1937. A fourth type of phakomatosis, Sturge-Weber syndrome. *Verh. Kon. Nederl. Akad. Wetens.* Sect. 2, 36, No. 4, pp. 33.

Bücklers, M. 1932. Über eine bisher unbekannte familiäre Starform. *Zeits. f. Augenhlk.* 77:139.

Bücklers, M. 1939. Zur Entstehung und Rückbildung des Zuckerstars. *Klin. Monatsbl. f. Augenhlk.* 102:465–472. Figs. 4.

Bühler, E. 1940. Die Oberliddeckfalte am Europäernauge. *Zeits. f. Morph. u. Anthrop.* 38:56–62. Pls. 3.

Cameron, E. P. 1926. An interesting example of hereditary dislocation of the lens occurring in four successive generations. *Brit. J. Ophth.* 10:384–386.

Campbell, Dorothy A. 1933. The chemical pathology of cataract. *Trans. Ophth. Soc. U. K.* 53:391–400.

———. 1936. Recent observations on the bio-chemistry of the lens. *Brit. Med. J.* ii. 1133–1136.

Catsch, A. 1939. Die fibrae medullares retinae des Menschen. *Zeits. f. Mensch. Vererb. u. Konst-lehre* 24:59–112. Figs. 11.

Chouke, K. S. 1929. The epicanthus or Mongolian fold in Caucasian children. *Am. J. Phys. Anthrop.* 13:255–279. Figs. 8.

Clarke, E. 1925. Genesis of myopia. *Trans. Ophth. Soc. U. K.* 45:373–386.

Clausen, W. 1923. Vererbungslehre und Augenheilkunde. *Zentlbl. f. Ophth.* 11:81–94, 209–218, 417–424, 481–498.

Cockayne, E. A. 1931. Epicanthus and bilateral ptosis. *Proc. Roy. Soc. Med.* 24:847–848. Fig. 1.

———. 1936. The inheritance of opaque nerve fibres in the retina (papilla leporina). *Brit. J. Ophth.* 20:569–575.

Cockburn, C. 1944. A case of cornea plana. *Brit. J. Ophth.* 28:486–488. Pl. 1.

Collier, W. T. 1931. Two cases of Lindau's disease. *Brit. Med. J.* ii. 144–145.

*Collins, T. 1900. *Trans. Ophth. Soc. U. K.* 20:90.

Coover, D. H. 1910. Cryptophthalmia. *J. Am. Med. Assn.* 55:371. Figs. 2.

Cotterman, C. W. & Falls, H. F. 1944. Genetic studies on ectopia lentis. II. Anthropometric and linkage data. *Ann. Eugen.* 12:158–168.

Courtney, R. H. & Hill, E. 1931. Hereditary juvenile glaucoma simplex. *J. Am. Med. Assn.* 97:1602–1609. Figs. 9.

Craft, W. A. 1927. Night-blindness in cattle. *J. Hered.* 18:215–216.

Curtius, F. & Decker, J. F. 1930. Erbliche Disposition bei rezidivierender Okulomotoriusparese. *Klin. Monatsbl. Augenhlk.* 84:773–788.

Cutler, C. W. 1895. Ueber angeborene Nachtblindheit und Pigmentdegeneration. *Arch. f. Augenhlk.* 30:92–116. Pls. 2.

Czellitzer, A. 1928. Die Vererbung hochgradiger Kurzsichtigkeit. *Verh. V. Internat. Kongr. Vererb.* 1:578–594.

Danforth, C. H. 1914. Some notes on a family with hereditary congenital cataract. *Amer. J. Ophth.* 31:161–172. Fig. 1.

Davenport, R. C. 1927a. A family history of choroidal sarcoma. *Brit. J. Ophth.* 11:443–445.

———. 1927b. Bilateral "macular coloboma" in mother and son. *Proc. Roy. Soc. Med.* 21:109–110.

Dax, E. C. 1940. Retinitis pigmentosa. *Quart. J. Med.* 33:263–307. Pl. 1.

DeHaas, H. L. 1931. Een familie met erfelijke ontaarding van de macula lutea. *Nederl. Tijdschr. v. Geneesk.* 75:4720–4721.

Detlefson, J. A. & Yapp, W. W. 1920. The inheritance of congenital cataract in cattle. *Amer. Nat.* 54:277–280.

Dimitry, T. J. 1921. Hereditary ptosis. *Amer. J. Ophth.* 4:655–658. Figs. 3.

Doggart, J. H. 1931. Epithelial dystrophy of the cornea. *Trans. Ophth. Soc. U. K.* 51:52–63. Pl. 1, figs. 2.

———. 1939. Two cases of familial keratitis. *Proc. Roy. Soc. Med.* 32:765–766.

Dollar, Jean M. 1938. Familial ptosis. *Proc. Roy. Soc. Med.* 31:1097–1098.

Dressler, M. 1937. Familiäres Vorkommen von Adieschen Syndrom mit Hippus. *Klin. Wochens.* 16:1013–1017. Figs. 3.

Duggan, J. N. & Nanavati, B. P. 1927. A family with blue sclerotics. *Brit. Journ. Ophthal.* 11:445–447.

Duke-Elder, Sir W. S. 1940. *Text-book of Ophthalmology.* London. 3 Vols.

Eaton, O. N. 1937. A hereditary eye defect in guinea pigs. *J. Hered.* 28:353–358. Figs. 2.

Ebert, R. H. 1943. Angioid streaks and pseudoxanthoma elasticum. *Arch. of Derm. & Syph.* 48:75–82.

Endelman, L. 1931. Zweiter und dritter Fall von Oguchischer Krankheit in Europe. *Klin. Mon. f. Augenhlk.* 87:798–801.

Erdmann, P. 1904. Ein Beitrag zur Kenntnis der Distichiasis congenita (hereditaria). *Zeits. f. Augenhlk.* 11:427–444. Pl. 1.

Falls, H. F. & Cotterman, C. W. 1943. Genetic studies on ectopia lentis. *Arch. of Ophth.* 30:610–620. Figs. 3.

Faulkner, S. H. 1939. Familial ptosis with ophthalmoplegia externa starting in adult life. *Brit. Med. J.* ii. 854.

Fecht, W. 1927. Über familiäre Linsenluxation. *Zeits. f. Augenhlk.* 62:162–168.

Fine, A. 1933. Familial bilateral ankyloblepharon. *Arch. of Ophth.* 10:821–824. Figs. 2.

Flach, F. 1942. A familial study in myopia. *J. Hered.* 33:456.

Flieringa, H. J. 1924. Familiäre Ptosis congenita kombiniert mit anderen angeboren Beweglichkeitsdefekten der Bulbusmuskulatur. *Zeits. f. Augenhlk.* 52:1–14. Figs. 26.

Folkar, H. H. 1909. Nodular opacity of the cornea in three generations. *Trans. Ophthal. Soc. U. K.* 19:42–54.

Ford, R. 1925. Two cases of congenital blepharophimosis. *Proc. Roy. Soc. Med.* (Ophth.) 18:15.

Fortuyn, A. B. D. 1932. Formation of single-ovum twins. *Quart. Rev. Biol.* 7:298–306. Figs. 3.

Franceschetti, A. 1930. *Die Vererbung von Augenleiden.* Berlin. Pp. 228.

Franceschetti, A. & Babel, J. 1944. Essai de classification anatomique des degenerescences familiales et héréditaires de la cornée. *Ophthalmologica* 107:66–72. Figs. 2.

Franceschetti, A. & Klein, D. 1941. Über das Vorkommen von hereditärer juveniler Maculadegeneration (Typ Stargardt) bei zwei Geschwisterpaaren der Friedreich-Sippe "Glaser." *Arch. J. Klaus-Stift.* 16:469–93. Pls. 4.

Freiberger, M. & Josephson, E. M. 1936. Hereditary corneal dystrophy. *Eugen. News* 21:103.

Froelich, R. E. 1924. Über Flocculus-Bildungen der menschlichen Iris und ihre Vererbung. *Arch. f. Rass. u. Ges.-Biol.* 15:249–262.

Frykholm, R. 1935. Familiäre Hornhautentartung, vererbt durch 6 Generationen, klinisch nachgewiesen bei 13 Mitgliedern der 3 letzten. *Klin. Mon. f. Augenhlk.* 94:76–81. Figs. 2.

Galloway, R. M. 1930. Hereditary lamellar cataract. *Brit. Med. J.* i. 149.

Garfunkel, B. 1926. Zur Erblichkeit der Kataracta senilis. *Arch. J. Klaus-Stift.* 2:71–78. Pls. 5.

Gasser, Ilse. 1938. Über Vererbung extremer Hornhautkrümmung. *Arch. J. Klaus-Stift.* 13:667–678.

Gassler, V. J. 1925. Über eine bis jetzt nicht bekannt recessive Verknüpfung von hochgradiger Myopie mit angeborener Hemeralopie. *Arch. J. Klaus-Stift.* 1:259–272.

Gayer, K. 1942. A study of coloboma and other abnormalities in transplants of eye primordia from normal and creeper chick embryos. *J. Exp. Zool.* 89:103–129. Pls. 2.

Gesell, A. & Blake, E. M. 1936. Twinning and ocular pathology. *Arch. of Ophth.* 15:1051–1071. Figs. 8.

Gilch, T. 1937. Über die Verbreitung und Vererbung der familiären Hornhautentartung in Württemberg. *Zeits. f. Mensch. Vererb. u. Konst.* 21:1–54.

Giri, D. V. 1936. Congenital bilateral ophthalmoplegia externa: a case helped by prisms. *Proc. Roy. Soc. Med.* 30:43–45.

———. 1944. Bilateral ptosis and atypical slant eyes associated with unilateral syndactyly, adactyly and brachyphalangy. *Proc. Roy. Soc. Med.* 37:360–361. Figs. 2.

Goedblad, J. 1942. Mode of inheritance of choroideremia. *Ophthalmologica* 104:308–315.

*Gray, H. 1944. Trichomegaly or movie lashes. *Stanford Med. Bull.* 2:157–158.

Gredig, C. 1926. Zur Erblichkeit der Katarakta senilis. *Arch. J. Klaus-Stift.* 2:71–78. Pls. 5, charts 29.

Greenthal, R. M. 1945. Congenital malformations in the infant caused by rubella early in pregnancy. *Arch. of Pediat.* 62:53–56.

Greenwood. A. 1931. Lattice keratosis: five cases in one family. *Arch. of Ophthal.* 5:497–498.

Gregory, P. W., Mead, S. W. & Regan, W. M. 1943. A congenital hereditary eye defect in cattle. *J. Hered.* 34:124–128. Fig. 1.

Griscom, J. M. 1921. Hereditary optic atrophy. *Amer. J. Ophth.* 4:347–352. Figs. 13.

Groenouw, Dr. 1933. Knötchenförmige Hornhautübungen vererbt durch vier Generationen. *Klin. Mon. f. Augenhlk.* 90:577–580.

Grönholm, V. 1921. Über die Vererbung der Megalocornea nebst einem Beitrag zur Frage des genetischen Zusammenhangs zwischen Megalocornea und Hydrophthalmus. *Klin. Monatsbl. f. Augenheilk.* 67:15. Figs. 4.

Gruenwald, P. 1944. The morphogenesis of a hereditary type of microphthalmia in chick embryos. *Anat. Record* 88:67–80. Pls. 2.

Guett, A. 1938. *Erbleiden des Auges; Handbuch der Erbkrankheiten*, Vol. 5. Pp. 310, pls. 221. Leipzig.

Gut, A. 1932. Über die Vererbung der physiologischen Papillen-excavation. *Arch. J. Klaus-Stift.* 7:281–297. Pls. 2.

Hagedoorn, A. 1939. Angioid streaks. *Arch. of Ophth.* 28:1020–1027. Fig. 1.

Hain, A. M. 1936. Microphthalmia and other eye-defects throughout fourteen generations of albino rats. *Proc. Roy. Soc. Edinb.* 57:64–77.

Halbertsma, K. T. A. 1928. Familiare juveniele cataract. *Nederl. Tijdschr. v. Geneesk.* 72:855–860.

———. 1932. Über Verbreitung und Vorkommen von Kolobomen und Lochbildung der Papille. *Genetica* 14:117–128.

———. 1934. Familiare aangeboren catarakt. *Nederl. Tijdschr. v. Geneesk.* 78:1705–1709.

Halbertsma, K. T. A. 1934. Familiare, erfelijke opticusatrophie. *Nederl. Tijdschr. v. Geneesk.* 78:4079–4090.

———. 1935. Distichiasis congénital vrai. *Arch. d'Ophth.* 52:738–748. Figs. 2.

Haldane, J. B. S. 1938. Congenital disease. *Lancet* 235:1449–1455.

Hale, F. 1933. Pigs born without eyeballs. *J. Hered.* 24:105–106. Fig. 1.

Harman, N. B. 1909. Congenital cataract: a pedigree of four generations. *Trans. Ophth. Soc. U. K.* 29:101–108.

———. 1910. Congenital cataract. *Treas. of Human Inher.* 4:126–166. Pls. 8.

Hartung, H. 1932. Ueber familiäre angioide Pigmentstreifenbildung des Augenhintergrundes. *Klin. Mon. f. Augenhlk.* 88:43–60. Figs. 12.

Hemmes, G. D. 1924. Over hereditairen nystagmus. Diss. Wageningen.

———. 1926. Über die Genese des hereditären Nystagmus. *Zeits. f. Augenhlk.* 58:413–418.

Hildén, K. 1938. On the relation between the age and the occurrence of the Mongolian eye-fold. *Soc. Sci. Fenn. Comment. Biol.* 7.

Hind, H. Y. 1863. *Explorations in the Interior of the Labrador Peninsula.* 2 Vols. London.

Hippel, E. v. 1930. Embryologische Untersuchungen über Vererbung angeborener Katarakt, über Schichtstar des Hundes sowie über eine besondere Form von Kapselkatarakt. *Arch. f. Ophth.* 124:300–324. Figs. 19.

Hoffmans, D. 1936. The inheritance of cataracts. *Eugen. News* 21:36.

Hogben, L. 1932. The genetic analysis of familial traits. III. Matings involving one parent exhibiting a trait determined by a single recessive gene substitution with special reference to sex-linked conditions. *J. Genet.* 25:293–314.

Holm, E. 1926. Hereditary nystagmus. *Acta Ophthal.* 4:20–27. Figs. 4.

Holth, S. & Berner, O. 1923. Congenital miosis or pinhole pupils owing to developmental faults of the dilator muscle. *Brit. J. Ophth.* 7:401–419. Figs. 15.

Hornbach, E. T. & deGaris, C. F. 1933. The inheritance of cataract in man, pedigree and interpretation. *J. Morph.* 54:347–363.

Huber, A. 1931. Ophthalmologische Untersuchungen an eineiigen und zweieiigen Zwillingen. *Arch. J. Klaus-Stift.* 6:41–122. Many figs.

———. 1943. Über angebliche Abnützungskrankheiten des Auges. *Arch. J. Klaus-Stift.* 18:17–86.

Huber, O. 1935. Stammbaum mit seltener Häufung von Katarakt. *Zeits. f. Augenhlk.* 85:310–313.

Hubert, W. H. de B. 1932. A pedigree showing an atypical form of hereditary optic atrophy exhibiting apparent polymorphism. *J. Neur. & Psychopath.* 13:32–44.

Iles, A. E. 1939. *Proc. Roy. Soc. Med.* 32:1614.

———. 1939. Von Hippel-Lindau's disease. *Proc. Roy. Soc. Med.* 32:1618.

Imai, Y. & Moriwaki, D. 1936. A probable case of cytoplasmic inheritance in man: a critique of Leber's disease. *J. Genet.* 33:163–167.

Inman, W. S. 1935. The emotional factor in the causation of diseases of the eye. *Trans. Ophth. Soc. U. K.* 55:423–434.

Ivanov. 1928. Hereditäre und familiäre Arteria hyaloidea persistens. *Russ. Ophth. J.* 7:757. (Cited from Waardenburg.)

Jablonski, W. 1922. Zur Vererbung der Myopie. *Klin. Mon. f. Augenhlk.* 68:560–573.

James, R. R. 1927. A pedigree of a family showing hereditary glaucoma. *Brit. Journ. Ophthal.* 11:438–443.

Jeffrey, F. P. 1941. Hereditary microphthalmia in the domestic fowl. *J. Hered.* 32:310–312. Fig. 1.

John, I. 1934. Ein Beitrag zur Vererbung der angeborenen unkomplizierten Blepharophimosis. *Graefe's Arch. f. Ophth.* 133:60–66. Figs. 4.

Josephson, E. M., Cameron, G. & Freiberger, M. 1936. Genetic dangers of dinitrophenol reduction therapy. *Eugen. News* 21:34–35.

Judd, J. H. 1933. Nodular degeneration of the cornea. *Am. J. Ophth.* 16:310–318. Figs. 5.

Junius, P. 1934. Angiomatosis retinae — Retinitis exsudativa Coats — Morbus Osler. *Zeits. f. Augenhlk.* 84:193–210.

Kamenetzki, S. G. F. 1925. Eine eigenartige hereditäre Glaukomform mit Mangel des Irisstromes und geschlechsgebundener Vererbung. *Klin. Mon. f. Augenhlk.* 74:133–150.

Kawakami, R. 1925. Über die Vererbung der Oguchischen Krankheit. *Klin. Mon. f. Augenhlk.* 72:340–349.

———. 1926. Beiträge zur Vererbung der familiären Sehnervenatrophie. *Graefe's Arch. f. Ophth.* 116:568–595.

Kayser, B. 1914a. Über den Stammbaum einer Familie mit Vererbung von Megalocornea nach dem Hornerschen Vererbungstypen. *Arch. f. Rass. Ges. Biol.* 11:170–173.

———. 1914b. Megalocornea oder Hydrophthalmus? Nebst einem Stammbaum mit 17 Patienten über 6 Generationen. *Klin. Monatsbl. f. Augenheilk.*, 52:226–239.

Keeler, C. E. 1927. Rodless retina, an ophthalmic mutation in the house mouse, *Mus musculus*. *J. Exp. Zool.* 46:355–401. Figs. 4, pls. 3.

———. 1928. Blind mice. *J. Exp. Zool.* 51:495–508. Figs. 10.

———. 1934. Hereditary blindness and the Howe Laboratory. *Eugen. News* 19:110–114.

Keith, Arthur. 1923. *Human Embryology and Morphology.* London. 4th ed.

Keith, Sir A. 1925. Myopia, a disorder of growth. *Lancet* i. 32–33.

Khan, W. A. 1926. Pedigree of lamellar cataract. *Brit. J. Ophth.* 10:387–389.

King, H. D. 1931. Studies on the inheritance of structural anomalies in the rat. *Amer. J. Anat.* 48:231–260.

*Kitihara, S. 1930. Über den angeborenen familiären Nystagmus (Japanese). *Acta Ophth. Japon.* 34:382–414.

Klainguti, R. 1923. Farbensinnstörung bei Retinitis pigmentosa and totale Farbenblindheit. *Schweiz. Med. Wochens.* 4:910–912.

———. 1932. Die tapeto-retinale Degeneration im Kanton Tessin. *Klin. Monatsbl. f. Augenhlk.* 89:253.

Kleiner, W. 1923. Über den grossen schweizerischen Stammbaum in dem mit Kurtzichtigkeit kombinierte Nachtblindheit sich forterbt. *Arch. f. Rass. u. Ges.-Biol.* 15:1–17.

deKleyn, A. 1938. Some remarks on vestibular nystagmus. *Proc. Kon. Neder. Akad. Wetens.* 41:552–555.

Komai, T. 1934. Pedigrees of hereditary diseases and abnormalities found in the Japanese race. *Kyoto.* Pp. 51, pls. 84.

Kredbová, P. 1932. Familiarni výskyt ectopia lentis. *Casop. lék. česk.* 71:871–873.

Kugelberg, L. 1934. Juvenile Katarakt bei Dermatosen. *Klin. Mon. f. Augenhlk.* 92:484–508.

Lambert, R. K. & McDonnald, C. E. 1931. Hereditary high hyperopia. *Am. J. Ophth.* 14:46–48.

Lange, F. 1936. Das tiefe und das oberflächliche Auge. *Münch. Med. Wochens.* 83:1559–1561. Figs. 21.

Langworthy, O. R. & Ortega, L. 1943. The iris. *Medicine* 22:287–361. Pls. 9.

Leber, Th. 1871. Ueber anomale Formen der Retinitis pigmentosa. *Arch. f. Ophth.* 17:314–341.

Lenz, F. 1932. Über die Geschlechtsgebundenheit des erblichen Augenzitterns. *Arch. f. Rass. u. Ges.-Biol.* 26:194–200.

Levit, S. G. 1936. The problem of dominance in man. *J. Genet.* 33:411–434.

Levy-Wolff, L. 1940. The pathogenesis of retinitis pigmentosa (sclerosis pigmentosa chorioretinalis). *Am. J. Ophth.* 23:275–285, 418–433.

Liepin, T. K. 1924. On the question of inheritance of short-sightedness (Russian). *Bull. Bur. Eugenics, Leningrad* 2:60–66.

Lindau, A. 1930. On the problem of angiomatosis retinae. *Acta Ophth.* 8:334–336.

Loeffler, L. 1932. Über eine Mutation bei der weissen Hausmaus, ihre Genetik und deren Bedeutung für die menschliche Erblehre. *Zeits. f. Abst. u. Vererb.* 61:409–446. Figs. 19.

Long, J. C. & Danielson, R. W. 1945. Cataract and other congenital defects in infants following rubella in the mother. *Arch. of Ophth.* 34:24–27.

*Lutman, F. C. & Neel, J. V. 1945. Inherited cataract in the B. genealogy. *Arch. of Ophth.* 33:358.

McBain, E. H. 1942. Hereditary corneal dystrophies. *Arch. of Ophth.* 28:1020–1027. Fig. 1.

Macklin, M. T. 1927a. Hereditary abnormalities of the eye. II. Inheritable defects involving the eyelids and their mode of transmission. *Canad. Med. Assn. J.* 17:55–60.

———. 1927b. III. Anomalies of the entire eyeball. *Can. Med. Assn. J.* 17:327–331, 421–423.

———. 1927c. IV. Heritable diseases affecting the conjunctiva. *Can. Med. Assn. J.* 17:697–702.

———. 1927d. V. Inheritable defects of the iris and lens. *Can. Med. Assn. J.* 17:937–942.

Macklin, M. T. 1927e. VI. Inheritable defects involving the retina. *Can. Med. Assn. J.* 17:1191–1197, 1336–1342.

McIlroy, J. H. 1929. Hereditary ptosis with epicanthus: a case with pedigree extending over four generations. *Proc. Roy. Soc. Med.* 23:285–288. Figs. 2.

McKinney, J. M. & Frocht, M. 1940. Adie's syndrome. *Am. J. Med. Sci.* 199:546–555. Figs. 8.

McQuarrie, M. D. 1935. Two pedigrees of hereditary blindness in man. *J. Genet.* 30:147–153.

Måhlén, S. 1942. Beitrag zur Kenntniss der Flocculi iridis. *Acta Ophth.* 20:153–158. Col. pl. 1.

Mann, Ida C. 1928. Retinitis pigmentosa and Leber's hereditary optic atrophy occurring in cousins. *Ann. of Eugen.* 3:77–83.

———. 1935. Congenital retinal fold. *Brit. J. Ophth.* 19:641–658. Figs. 14.

Mann, I. & Kilner, T. P. 1943. Deficiency of the malar bones with defect of the lower lids. *Brit. J. Ophth.* 27:13–20. Figs. 4.

Manson, J. S. 1912. Hereditary lamellar cataract and digital deformity in the same pedigree. *Trans. Ophth. Soc. U. K.* 32:45–53.

———. 1928. *Observations on Human Heredity.* Lewis and Company, London.

Mayou, M. S. 1904. Cerebral degeneration, with symmetrical changes in the maculae, in three members of a family. *Trans. Ophth. Soc. U. K.* 24:142–145.

Meirowsky, Dr. 1926. Kleinere Mitteilungen zur Erblichkeitslehre. *Arch. f. Rass. u. Ges.-Biol.* 17:414–417.

Merritt, H. H. 1930. Hereditary optic atrophy (Leber's disease). *Arch. Neur. & Psychiat.* 24:775–781.

Meumann, E. 1928. Uber die nicht-kongenitale Form der hereditären Ptosis. *Arch. f. Augenhlk.* 99:661–669.

Meyerhof, Max. 1928. The book of the ten treatises on the eye ascribed to Hunain Is-Hâq (807–877 A.D.). Cairo Govt. Press. Pp. 227 & Arabic text.

Mitchell, H. S. & Dodge, W. M. 1935. Cataract in rats fed on high lactose rations. *J. of Nutrition.* 9:37–49.

Moore, R. F. 1924. Physiology and pathology of the pupil reactions. *Trans. Ophth. Soc. U. K.* 44:38–43.

———. 1932. The non-luetic Argyll-Robertson pupil. *Trans. Ophth. Soc. U. K.* 51:203–209.

Morgan, O. G. & Batten, R. 1930. Angioid streaks in the retina. *Proc. Roy. Soc. Med.* 23:1005–1006.

Morton, A. S. 1893. Two cases of hereditary congenital night-blindness without visible fundus change. *Trans. Ophth. Soc. U. K.* 13:147–150. Figs. 5.

Motolese, A. & Berardi, M. 1936. Hornhautastigmatismus und Vererbung. *Arch. f. Ophth.* 136:27–39.

Müller, H. K. 1931. Kongenitales Entropium durch Epiblepharon. *Klin. Mon. f. Augenhlk.* 87:184–190. Figs. 5.

Mutch, J. R. 1944. Hereditary corneal dystrophy. *Brit. J. Ophth.* 28:49–86. Figs. 6.

Nachtsheim, H. & Gürich, H. 1939. Erbleiden des Kaninchenauges. I. Erbliche Nahtbändchentrübung der Linse mit nachfolgendem Kernstar. *Zeits. f. Vererb. u. Konst.* 23:463–483. Figs. 9.

Neame, H. 1945. Retinitis punctata albescens. *Proc. Roy. Soc. Med.* 37:686.

Neher, E. M. 1938. Aniridia congenita irideremia. *Am. J. Ophth.* 21:293–298.

Nettleship, E. 1907. A history of night-blindness in nine consecutive generations. *Ophth. Rev.* 26:250–251.

———. 1909. On some hereditary diseases of the eye. *Trans. Ophth. Soc. U. K.* 29:57–198. Figs. 69, 110 pedigrees.

———. 1912. A pedigree of congenital night-blindness with myopia. *Trans. Ophth. Soc. U. K.* 32:21–45.

Nettleship, E. & Ogilvie, F. M. 1906. A peculiar form of hereditary congenital cataract. *Trans. Ophth. Soc. U. K.* 26:191–207.

Nevin, S. 1933. Leber's disease. *Proc. Roy. Soc. Med.* 26:852.

Newman, H. H. 1913. Five generations of congenital stationary night-blindness in an American family. *J. Genet.* 3:25–38.

Niccol, W. 1938. A family with bilateral development defects at the macula. *Trans. Ophth. Soc. U. K.* 58:763–769.

Nordgren, G. 1936. Bidrag till frågan om sambandet mellan den allmänna hälsovården och myopifrekvensen bland skolbarn. *Nord. Med. Tidskr.* 12:2069–2076.

O'Connor, M. 1936. Palpebral pigmentation. *Eugen. News* 21:36.

Oguchi, C. 1907. Über einen Fall von eigenartiger Hemeralopie. *Nippon Gank. Zaschi* 11:123. (Cited from Waardenburg.)

———. 1926. Weitere Mitteilung über die Oguchische Krankheit. *Arch. f. Ophth.* 117:208–218.

Oswald, Agnes. 1911. Hereditary tendency to defective sight in males only of a family. *Brit. Med. J.* i. 18.

Page, H. 1874. Transmission through three generations of microphthalmos, irideremia and nystagmus. *Lancet* ii. 193–194.

Panneton, Ph. 1936. Le blépharo-chalazis, à propos 51 cas dans une même famille. *Arch. d'Ophth.* 53:729–755.

Panse, F. 1937. Über erbliche Zwischenhirnsyndrome und ihre entwicklungsphysiologischen Grundlagen. *Zeits. f. Neur. u. Psychiat.* 160:1–72.

Peters, R. 1915. Angeborener Lagophthalmus in vier Generationen. *Klin. Monatsbl. f. Augenhlk.* 55:308–313.

———. 1918. Auffallende Dunkelfärbung der unteren Lider als erbliche Anomalie. *Centlbl. f. prakt. Augenhlk.* 42:8–11.

Piennett, M. G. 1936. The inheritance of abnormal-looking eyes due to small palpebral fissure. *Eugen. News* 21:35.

Pines, I. L. Ja, & Tron, F. 1925. Hereditäre Neuritis optica (Lebersche Sehnervenatrophie). *Zeits. f. Neur. u. Psychiat.* 95:762–776. Figs. 5.

Pittenger, B. N. 1935. Ectopia lentis, 22 cases in 5 successive generations. *Arch. of Ophth.* 13:1051–1055.

*Poljok, B. L. & Popova, F. A. 1929. On the question of the pathogenesis of family inflammation of the tear duct (Russian). *Vrac. Gazeta.*

Pollnow, L. 1933. Über familiäre Beziehungen bei der Retinitis circinata. *Zeits. f. Augenhlk.* 81:164–168.

da Pozzo, E. 1938. Distichiasis congenita vera. *Boll. d'ocul.* 17:1015–1034. Figs. 5.

Punnett, R. C. 1933. An ocular Mendelian puzzle. *Trans. Ophth. Soc. U. K.* 53:9–16.

Regan, W. M., Gregory, P. W. & Mead, S. W. 1944. Hereditary strabismus in Jersey cattle. *J. Hered.* 35:233–234.

Richner, H. 1938. Hornhautaffektion bei Keratoma palmare et plantare hereditarium. *Klin. Mon. f. Augenhlk.* 100:580–588. Figs. 6.

Riddell, W. J. B. 1940. A pedigree of hereditary stationary sex-linked night-blindness. *Ann. of Eugen.* 10:326–331.

———. 1941. Uncomplicated hereditary megalocornea. *Ann. of Eugen.* 11:102–107.

Riegel, E. 1933. Ueber familiäre Hornhautentartung. *Klin. Mon. f. Augenhlk.* 90:498–504.

Roberts, J. A. F. 1937. Sex-linked microphthalmia sometimes associated with mental deficiency. *Brit. Med. J.* ii. 1213–1216.

———. 1940. *An Introduction to Medical Genetics.* Oxford Press. Pp. 266.

Rodin, F. H. 1926. A family of squinters. *J. Am. Med. Assn.* 86:1613–1614. Fig. 1.

———. 1934. A family of squinters. *Arch. of Ophth.* 12:874–876. Fig. 1.

———. 1936. Report of a pedigree of 4 generations of hereditary congenital ptosis affecting only one eye and a pedigree of one generation of congenital ptosis with epicanthus. *Amer. J. Ophth.* 19:597–599. Figs. 2.

Roese, H. F. 1933. Eine durch vier Generationen vererbte angeborene Linsenektopie. *Zeits. f. Augenhlk.* 81:149–155.

Romer, A. 1926. Untersuchung über die Erblichkeit der Spiesskatarakt (Vogt). *Arch. J. Klaus-Stift.* 2:207–220. Pls. 2.

Ross, N. 1932. Congenital epicanthus and ptosis transmitted through four generations. *Brit. Med. J.* i. 378–379.

Routil, R. 1933. Von der Richtung der Augenlidspalte. *Zeits. f. Morph. u. Anthrop.* 32:469–482.

Rozprým, F. & Suk, V. 1934. Eyebrows and eyelashes in man. *J. Roy. Anthrop. Inst.* 64:353–395.

Rudolf, G. de M. 1936. Tonic pupils with absent tendon reflexes in mother and daughter. *J. Neur. & Psychopath.* 16:367–376.

Rush, C. C. 1926. Congenital aniridia. *Trans. Am. Ophth. Soc.* 24:332–341.

Russell, W. R. 1931. Hereditary aspects of Leber's optic atrophy. *Lancet* 221:1018–1020.

———. 1932. Hereditary aspects of Leber's optic atrophy, with a report of cases consequent upon the mating of cousins. *Trans. Ophth. Soc. U. K.* 51:187–202.

Sala, G. 1932. Su di alcune malformazioni oculari a tipo ereditario e familiare. *Rasseg. ital. d'ottal.* 1:622–632.

Sander, P. 1931. A family affected with keratoconus and anterior polar cataract. *Brit. J. Ophth.* 15:23–25.

Savin, L. H. & Sorsby, A. 1935. Two brothers, members of a family with "lobster-claw," one showing the skeletal deformity and the other aniridia. *Proc. Roy. Soc. Med.* 28:525.

Schappert-Kimmijser, J. 1933. Rezidivierende Hornhauterosion und familiäre Hornhautentartung. *Klin. Mon. f. Augenhlk.* 90:655–661.

Scheie, H. G. 1940. Site of disturbance in Adie's syndrome. *Arch. of Ophth.* 24:225–237. Figs. 3.

Scheurlen, W. 1935. Ueber die Vererbung der Pigmentdegeneration der Netzhaut und ihre Verbreitung in Württemberg und Hohenzollern. *Klin. Mon. f. Augenhlk.* 94:761–792.

Schnyder, W. F. 1920. Über familiares Vorkommen resp. die Vererbung von Erkrankungen der Tränenwege. *Zeits. f. Augenhlk.* 44:257–261.

Schönenberger, F. 1926. Beitrag zur Kenntnis der homochronhereditären Opticusatrophie. *Arch. J. Klaus-Stift.* 2:59–70.

*Schutz, S. 1943. Hereditary corneal dystrophy: history of condition and presentation of a pedigree. *Arch. of Ophth.* 29:523–534.

Scott, J. G. 1945. The eye of the West African negro. *Brit. J. Ophth.* 29:12–19.

Sedan, Dr. 1885. Une famille d'héméralopes. *Rec. d'Ophth.* 3rd Ser. 7:675–678.

Sedgwick, W. 1861. On sexual limitation in hereditary disease. *Brit. & Foreign Med.-Chirurg. Rev.* 27:477–498. 28:198–214.

Sicherer, V. 1907. Vererbung des Schielens. *Münch. Med. Woch.* 54:1231–1232.

Siemens, H. W. 1925. Ueber einen, in der menschlichen Pathologie noch nicht beobachteten Vererbungsmodus: dominant-geschlechtsgebundene Vererbung. *Arch. f. Rass. u. Ges.-Biol.* 17:47–61.

Smith, S. E. & Barrentine, B. F. 1943. Hereditary cataract, a new dominant gene in the rat. *J. Hered.* 34:8–10. Fig. 1.

Snell, S. 1903. Numerous instances of night-blindness (retinitis pigmentosa) occurring in five generations, with genealogical chart. *Trans. Ophth. Soc. U. K.* 23:68–70.

———. 1908. Coloboma of the iris in each eye, occurring in five generations. *Trans. Ophth. Soc. U. K.* 28:148–150.

Sorsby, A. 1934. Anophthalmos: an unpublished manuscript by James Briggs giving the first account of the familial occurrence of the condition. *Brit. J. Ophth.* 18:469–472.

———. 1934. Familial occurrence of macular coloboma associated with apical dystrophy of hands and feet. *Proc. Roy. Soc. Med.* 27:694–699.

———. 1935. Congenital coloboma of the macula together with an account of the familial occurrence of bilateral macular coloboma in association with apical dystrophy of hands and feet. *Brit. J. Ophth.* 19:65–90. Figs. 20.

———. 1935. Ocular lesions in bony dystrophies. *Trans. Ophth. Soc. U. K.* 55:499–506.

Srinivasan, E. V. 1931. A family of Groenouw's dystrophy. *Brit. J. Ophth.* 16:296.

Stahlin, S. 1931. Gibt es eine erbliche Sehnervenatrophie ausser der Leberschen Atrophie? *Arch. f. Augenhlk.* 104:222–263.

Steggerda, M. 1928. Hereditary nystagmus. *Eugen. News* 13:7.

Stephenson, W. V. 1945. Anterior megalophthalmos and arachnodactyly. *Am. J. Ophth.* 28:315–317.

Steyn, J. S. 1926. Familial juvenile degeneration of the macula. *Brit. J. Ophth.* 10:391–395. Fig. 1.

Stieren, E. 1907. A study in atavistic descent of congenital cataract through 4 generations. *Ophth. Rec.* 16:234–238.

Stuckey, H. P. 1916. The slit-eyed people. *J. Hered.* 7:147. Pl. 1.

Suk, V. & Rozprym, F. 1931. Eyebrows and eyelashes in man: their different forms, pigmentation and heredity. *Publi. de la Fac. Sci. Univ. Masaryk*, Prague. Pp. 10, figs. 19.

*Swan, C. *et al.* 1943. *Med. J. Australia* 2:291.

Swanzy, H. R. 1873. Cases of congenital hemeralopia. *Irish Hosp. Gaz.* 1:84–86.

Szily, A. von. 1924. Die Ontogenese der idiotypischen (erbbildlichen) Spaltbildungen des Auges, des Mikrophthalmus und der Orbitalcysten. *Zeits. f. Anat. u. Entw-gesch.* 74:1–230. Figs. 175.

Szily, A. von & Eckstein, A. 1923. Vitaminmangel und Schichtstargenese. *Klin. Mon. f. Augenhlk.* 71:545–583. Figs. 15.

Tatham, T. J. 1890. Note on a case of hereditary tendency to cataract in early childhood. *Trans. Ophth. Soc. U. K.* 10:141–145.

Theodore, F. H. 1944. Congenital opacities of the cornea. *Arch. of Ophth.* 31:138–143. Figs. 7.

Thompson, H. & Cashell, G. T. W. 1935. A pedigree of congenital optic atrophy embracing sixteen affected cases in six generations. *Proc. Roy. Soc. Med.* 28:1415–1425. Figs. 14.

Thomsen, Chr. 1915. Ueber die Vererbung des Microphthalmus mit und ohne Katarakt. *Klin. Monatsbl. f. Augenheilk.* 54:236–249.

Thomson, E. & Ballantyne, A. J. 1903. Congenital bilateral pigmentation of the cornea. *Trans. Ophth. Soc. U. K.* 23:274–276.

———. 1927. Krukenberg's spindle. *Brit. J. Ophth.* 11:450–451.

Town, A. E. 1943. Congenital absence of lacrimal puncta in three members of a family. *Arch. of Ophth.* 29:767–771. Figs. 2.

Tritscheller, L. 1921. Beitrag zur Vererbung der familiären Hornhautentartung. *Klin. Mon. f. Augenhlk.* 66:579–581.

Usher, C. H. 1924. A pedigree of congenital dislocation of lenses. *Biometrika* 16:273–282.

———. 1925. A pedigree of epicanthus and ptosis. *Ann. of Eugen.* 1:128–138. Pls. 4.

———. 1927. Two pedigrees of hereditary optic atrophy. *Brit. J. Ophth.* 11:417–437.

———. 1930. Two pedigrees of retinitis pigmentosa. *Ann. of Eugen.* 4:215–231.

———. 1932. Hereditary entropion and hereditary changes in the skin of the eyelids. *Biometrika* 24:1–20. Pls. 4.

———. 1933. Heredity and eye diseases. *Trans. Ophth. Soc. U. K.* 53:16–29.

Usher, C. H. 1935a. Pedigrees of hereditary epicanthus. *Biometrika* 27:5–25.

———. 1935b. On a few hereditary eye affections. *Trans. Ophth. Soc. U. K.* 55:164–245.

Vail, D. T. 1931. Adult hereditary anterior megalophthalmus sine glaucoma. *Arch. of Ophth.* 6:39–62. Figs. 12.

Van der Hoeve, J. 1932. Eye symptoms in phakomatoses. *Trans. Ophth. Soc. U. K.* 52:380–401.

Varelmann, H. 1925. Die Vererbung der Hemeralopie mit Myopie. *Arch. f. Augenhlk.* 96:385–405.

Veit, G. 1940. Über eine Familie mit Leberscher Opticusatrophie und Taubstummheit. *Zeits. f. Mensch. Vererb. u. Konst.* 24:620–647.

Verhoeff, F. H. 1942. Retinitis pigmentosa with widespread gliosis — so-called choroideremia. *Arch. of Ophth.* 27:688–691.

Verschuer, O. v. 1930. Vom Umgang der erblichen Belastung im deutschen Volke. *Arch. f. Rass. Ges. Biol.* 24:238–267.

Vignes, M. 1889. Epicanthus héréditaire. *Rec. d'Ophthal.* 3rd ser. 11:422–425.

Vinsonhaler, F. & Cosgrove, K. W. 1936. Hereditary cataract of the senile and presenile types. *Arch. of Ophth.* 15:222–224.

Vogt, A. 1905. Dislocatio lentis spontanea als erbliche Krankheit. *Zeits. f. Augenhlk.* 14:153–165.

———. 1922. Über geschlechtsgebundene Vererbung von Augenleiden. *Schweiz. Med. Wochens.* 52:77–83.

———. 1923. Weitere Ergebnisse der Spaltlampenmikroskopie des vorderen Bulbusabschnittes. VIII. Über die pathologisch veränderte Iris. *Graefe's Arch.* 111:91–127. Col. figs. 28.

———. 1925. Über Maculalosigkeit bei isoliertem Bulbusalbinismus als geschlechtsgebunden-rezessives Merkmal. *Arch. J. Klaus-Stift.* 1:119–122.

———. 1934. Neuer Stammbaum von Keratoconus (bei Cousines Germaines). *Zeits. f. Augenhlk.* 84:20.

———. 1938. Weitere Augenstudien an einiigen Zwillingen höheren Alters über die Vererbung der Altersmerkmale. *Klin. Mon. f. Augenhlk.* 100:497–544. Figs. 123 (many in color).

Vogt, A. & Meyer, G. 1937. Aufdeckung eines Stammbaumes von E. von Hippel'scher Angiomatosis retinae in der Schweiz. *Arch. J. Klaus-Stift.* 12:575–586. Pls. 4.

Vogt, A., Wagner, H., Richner, H. & Meyer, G. 1939. Das Senium bei einiigen und zweieiigen Zwillingen. *Arch. J. Klaus-Stift.* 14:475–597. Figs. 118.

Waardenburg, P. J. 1924a. Over een recessieven vorm van aangeboren ophthalmoplegie. *Genetica* 6:487–492.

———. 1924b. Over het erfelijkheidsmoment bij de aangeboren verplaatsing van de pupil en van de lens. *Genetica* 6:337–382. Figs. 14.

———. 1930. Die Zurückführung einer Reihe erblich-angeborener familiärer Augenmissbildungen auf eine Fixation normaler fetaler Verhältnisse. *Arch. f. Ophth.* 124:221–229. Figs. 37.

Waardenburg, P. J. 1932. Das menschliche Auge und seine Erbanlagen. *Bibliogr. Genet.* 7:1–631. Figs. 197.

———. 1935. Vererbungsergebnisse und -probleme am menschlichen Auge. *Zeits. f. Abst. u. Vererb.* 70:358–376.

———. 1936. Über familiärerbliche Fälle von seniler Maculadegeneration. *Genetica* 18:38–46.

———. 1938. (Hereditary nystagmus reappearing in the offspring of apparently discordant monozygotic twins.) *Nederl. Tijdschr. v. Geneesk.* 82:4512–4515.

———. 1942. Choroideremie als Erbmerkmal. *Acta Ophth.* 20:235–274. Figs. 5.

Weissenberg, S. 1927. Erbliche Nervenkrankheiten. *Arch. f. Rass. u. Ges.-Biol.* 19:425–426.

———. 1928. Zur Stammbaumkasuistik. *Arch. f. Rass. u. Ges.-Biol.* 20:428–432.

Wen, I. C. 1934. The development of the upper eyelid of the Chinese with special reference to the Mongolic fold. *Chinese Med. J.* 48:1216–1227. Figs. 13.

Werkle, F. 1931. Beitrag zur Kenntnis des Krankheitsbildes der progressiven Aderhautatrophie mit Pigmentdegeneration der Netzhaut. *Klin. Mon. f. Augenhlk.* 87:173–183. Pls. 2.

Werner, S. 1928. Erblicher Star und feingelocktes Haar bei mehreren Mitgliedern derselben Familie. *Acta Ophthal.* 6:382–389. Figs. 8.

West, L. S. 1939. Coincident inheritance of strabismus and nystagmus. *J. Hered.* 30:496–498.

Weve, H. 1935. Über "Ablatio falciformis cong." *Arch. f. Augenhlk.* 109:371–394. Figs. 15.

White, B. V., Jr. & Fulton, M. N. 1937. A rare pupillary defect inherited by identical twins. *J. Hered.* 28:177–179. Figs. 4.

*White, J. W. 1945. Congenital and hereditary abnormalities of the extra-ocular muscles. *N. Carolina Med. J.* 6:244.

von Wibaut, F. 1931. Studien über Retinitis pigmentosa. (I. Statistische Gründe für die Annahme, dass die R. p. in genetischem Sinn keine Einheit darstellt.) *Klin. Mon. f. Augenhlk.* 87:298–307. Pl. 1.

Wieser, St. 1927. Sehschärfe und Refraktion bei 46 Sudannegern. *Arch. J. Klaus-Stift.* 3:85–94.

Wilson, J. A. 1935. Ametropia and sex. *Brit. J. Ophth.* 19:613–614.

Wolff, E. 1930. A microphthalmic family. *Proc. Roy. Soc. Med.* 23:623–625.

Wolfsohn-Jaffé, Else. 1935. Ueber 9 Fälle von hereditärem Glaukom der Erwachsenen in 3 Generationen. *Klin. Mon. f. Augenhlk.* 94:662–668.

Wood, C. A. 1917. *The Fundus Oculi of Birds, Especially as Viewed by the Ophthalmoscope.* Chicago. Pp. 180, pls. 61.

Worth, C. 1906. Hereditary influence in myopia. *Trans. Ophth. Soc. U. K.* 26:141–144.

Wright, R. E. 1935. Familial macular degeneration. *Brit. J. Ophth.* 19:160–165. Pls. 2.

Yamazaki, Z. 1927. Beiträge zur Vererbung der Kurzsichtigkeit. *Zeits. f. Augenhlk.* 62:49–56.

Zilva, S. S., Golding, J., Drummond, C. J. & Coward, K. H. 1921. The relation of the fat-soluble factor to rickets and growth in pigs. *Biochem. J.* 15:427–437. Pl. 1.

Zorab, A. 1932. Glaucoma simplex familiaris. *Trans. Ophth. Soc. U. K.* 52:446–460.

Chapter VIII

HEREDITARY VARIATIONS AND ABNORMALITIES OF THE EAR

EARS are a feature which has been relatively little studied from a genetic point of view. Dahlberg (1926) made an extended record of ear shapes, with photographs in twins, showing that many small details of conformation must be inherited. Hildén (1922) gives three good pedigrees of *adherent ear lobes*, from Rüno Island off the coast of Riga. He finds the condition recessive to free ear lobes. Attached ear lobe was formerly regarded as a stigma of criminality or insanity, but Hildén shows that there is no connection with any mental or physical abnormality. Adherent or absent ear lobes is characteristic of Bushmen and Tierra del Fuegans and lobes are characteristically absent in Negroes; offstanding ears are seen in Kabyle, Kalmuck, Turkoman and Bashkir. The frequency of adherent ear lobes in Germany is 10 to 25 per cent.

Riddell (1942), in a study of eye color, recorded the ear lobes and occipital hair whorls in five hundred persons. He found a significant excess of women with attached lobes. One woman had one attached and one free lobe. There were 23 per cent of attached lobes in the group examined.

In a further study, Quelprud (1934a) confirms Hildén in some families but finds the conditions more complicated in others. Adherent lobes are more frequent in women, the percentages being 7 in men and 12 in women or roughly 2 : 1. The lobe may be from one-third to entirely adherent. When both parents have adherent lobes no child will be less than three-fifths adherent; when the parents' ear lobes are less than three-fifths adherent, no child will have completely adherent lobes. Wiener (1937) examined 124 families with 607 children. He recognized four grades of attachment and found all gradations between free and attached lobes. This condition may be due to multiple factors or to a main factor with modifiers. That the difference between free and attached ear lobes is a simple Mendelian pair in some families, with the former dominant, is indicated by the pedigree of Powell and Whitney (1937). In one family all eighteen members in three generations, except two wives from other families, had free ear lobes. Another family of seven members in three generations had attached ear lobes. Intermarriage of a member from each family resulted in a family of six, all with free ear lobes. This shows dominance, without evidence of segregation. Quelprud (1941) claims that adherent lobe, after "sex and age correction," is really dominant, which goes to show the dangers of statistical treatment insufficiently checked by the study of pedigrees.

Hildén (1929) made a study of Darwin's ear point or tubercle in the population of Finland. In various people the infolded edge of the helix has a more or less conspicuous projecting point which Darwin (*Descent of Man*) regarded as a remnant of the erect, pointed ears of our anthropoid ancestors. Schwalbe recognized six stages in the condition, from the most extreme everted point (Macacus form) to its complete absence, and Keith showed the existence of a chain of intermediate forms. Hildén examined this point in the ears of the pupils in two Finnish and two Swedish schools in Helsingfors, numbering in all 2077 children with 4154 ears. Forty of these ears (less than 1 per cent) belonged to the extreme Macacus form, 187 belonged to form three, with a typical inturned point or tubercle, and in 2215 ears there was no trace of the tubercle. Darwin's tubercle in one of its five forms was present in 50 per cent of the boys and 43 per cent of the girls. This excess of the more primitive ear form in boys was chiefly due to the Swedish boys, there being only a slight excess of its frequency in Finnish boys. Darwin quotes Meyer as also recording the tubercle more frequently in men than in women.

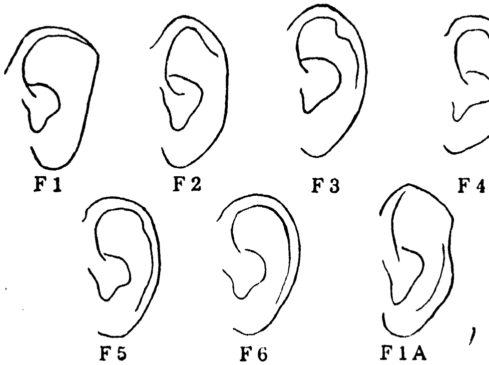

Fig. 86. Types of ear. (After Regmunt-Sobieszczanski)

When present in only one ear, Darwin's tubercle was rather surprisingly found to be twice as frequent in the right as in the left, the greater reduction of this condition in the left ear applying consistently to both the boys and the girls of each race independently. It was also found that the five types of Darwin tubercle were consistently more frequent in Swedish than in Finnish children. This difference is ascribed to the different proportions of the East Baltic and Nordic races in the two peoples. Its frequency in Germany (Haike, 1930) ranges from 15 to 25 per cent and in England it may be as high as 55 per cent, but much depends upon the definition.

Schwalbe's six types of ear margin are represented in Fig. 86. Regmunt-Sobieszczanski (1933) recognized a new type which he places between Schwalbe's types 1 and 2. In this type the upper and part of the lateral border of the helix, where Darwin's tubercle is situated, is unrolled, the uppermost part being the satyr point. In 1612 observations this form was found twice, bilaterally in a man of twenty-five and in the right ear of a girl of fourteen. Keith (1906) recorded the frequency of the "orang," "chimpanzee" and "gorilla" types of ear in Europeans.

An unrolled portion between the top of the ear and Darwin's tubercle is found by Geyer (1928) to be a sex-limited recessive, more frequent in men than boys. Bent-over helix between Darwin's tubercle and the ear lobe is more frequent in women, but the inheritance is uncertain because of shifting conditions. According to Haike (1930), the satyr point, a kink in the upper margin of the helix, normally persists to the second or third month *in utero*, and Darwin's point to the sixth month.

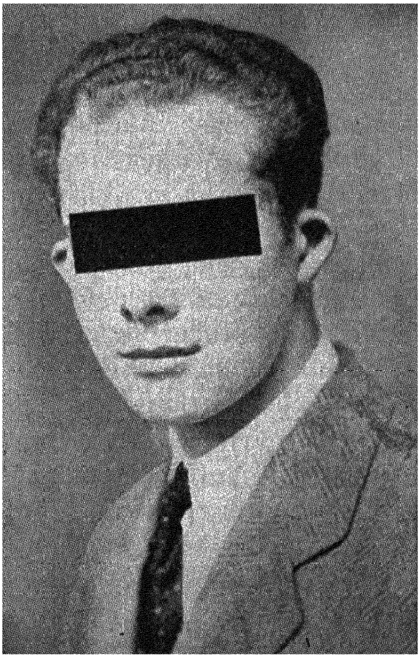
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Fig. 87. Cup-shaped ears. (After Potter) (From the *J. of Heredity*)

The inheritance of macroty (big ears), microty (small ears) and out-standing ears has been little studied. The anthelix may also be enlarged and protruding. When the enlarged portion connects with the helix it forms the Mozart ear, present in Mozart and his father. Cat ear is a persisting foetal condition of the third month, in which the upper posterior part of the helix is rolled over. Cup-shaped ear

(Fig. 87) may be the same, but cat's ear is found to be associated with ptosis. Helix flat in the upper part and connected with the anthelix (Fig. 88) was found in mother and daughter. The helix may have a nick in its posterior border, but the inheritance of this condition is unknown.

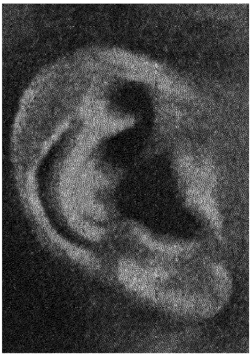

Fig. 88. Helix flat in upper part and connected with anthelix. (After Haike)

Quelprud (1934b) recognized six degrees in the development of Darwin's tubercle as well as the Cercopithecus and the Macacus or satyr type. From three pedigrees it appears to be inherited as an irregular dominant in one or both ears, occasionally occurring in a child when both parents were without it. From examination of 1524 persons in Germany, it was found that the tubercle generally increases with age in males and decreases in females. Quelprud confirmed that the right ear is more frequently affected and found the tubercle generally more developed on the right ear. Twin studies confirmed the inheritance. Another study of ears (Quelprud, 1932) shows that they are very similar in details of form in identical twins. In a summary of results he finds (1941) that males at all ages have larger ears than females, except in length of lobe and breadth of concha in which they are equal. Fistula auris congenita, crus cymbae, crus anthelicis in cymbam, auricular drops and certain ear deformities were found to be dominant; tuberculum anthelicis, tuberculum helicis fossale, crus anthelicis tertium and a bandlike helix were recessive.

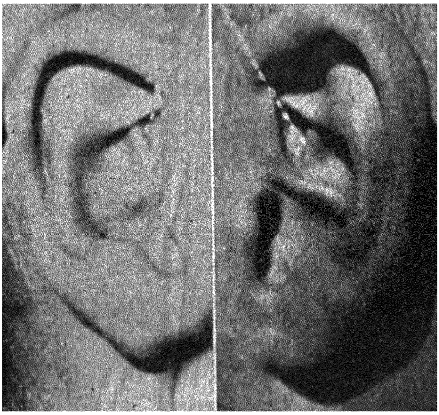

Fig. 89. Crus cymbae, a ridge in the concha. (After Quelprud)

A vertical cartilaginous ridge in the concha, which Quelprud (1934a) calls the *crus cymbae* (Fig. 89), is found in 5 to 6 per cent of ears and is dominant in many families, with considerable variation. Further family and twin studies (1939) show its irregular dominance and very variable expression. At the back of the ear a projecting cartilaginous lump is sometimes present (Fig. 90). It is more frequent in men, the sex-ratio being 72 : 29 per cent, but its manner of inheritance is unknown.

According to Bean (1915) human ears are decreasing in size and changing in shape. The ear undergoes retrograde metamorphosis before birth. Negroes have the smallest ears of any race. The Asiatic yellow-brown races have the largest and least retrograde, the Kalmucks and Patagonians being credited with the largest ears of all. The ears of the white race are intermediate, being longer than those of the Negro and about the same breadth. The length-breadth index of Topinard is therefore higher in the Negro. Bean finds the Negro ear small, almost flat, close to the head, with a broad helix as if much folded over. The satyr tubercle is found to be well marked while Darwin's tubercle is small or absent. The involuted ear, which is frequent in Negroes and Hottentots, is seldom found in whites. It has a broad helix much rolled in, frequently with a gnarled or crumpled appearance as if the result of injury, but not due to accident. The lobule is absent or small more frequently in Negroes and Filipinos, most frequently present in whites, Asiatics being intermediate. The ears are glabrous in Negroes, hirsute in whites, the Negro ear being most advanced in regressive evolution. Ears continue to increase in size with age to seventy years and beyond, this growth being more marked in white men than women. Bean has an elaborate classification of ear types, beginning with hypo, meso and hyper forms, which does not appear to have been adopted. He also (1909) studied Filipino ears and attempted to classify them on a racial basis.

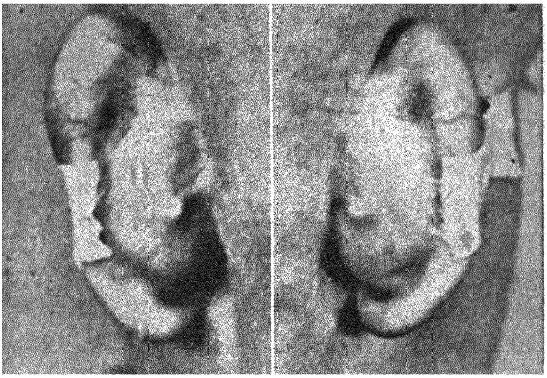

Fig. 90. Cartilaginous projection at back of ear. (After Quelprud)

Hypertrichosis of the ears is a striking abnormality described by Tommasi (1907).[1] A dense growth of long black hairs, beginning at eighteen to nineteen years, covers the anterior surface and the lower part of the posterior surface and remains black, even at eighty-one years of age. As shown in Fig. 6, p. 13, all the males (eleven cases) and no females were affected in five generations (except the twins, who were too young to show the character). This holandric inheritance follows the Y-chromosome, which must therefore contain the determining gene. Several members of this family were alcoholics, the proband and his sister were apparently sterile and became insane. The author reviews earlier studies of ears and of hypertrichosis.

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[1] Only the second paper gives data from which a pedigree can be constructed.

Various other inherited abnormalities of the ear have been described, both in man and animals. *Absence of the external ear* is cited (Windle, 1891) in a case where a normal father had a son with the defect. The father's male cousin had the defect, and two of his male children, but a daughter was normal. He quotes the case of a woman, two of her daughters and two granddaughters with "rudimentary lobules" to their ears, the male children and grandchildren being normal. Sedgwick (1861) cites a case of a boy with no external left ear, the meatus being imperforate. This boy's father had a male cousin whose two sons exhibited a deficiency of the cartilage of the left ear, while the daughter was normal. The manner of inheritance is not clear, except that it is from the original great-grandparents, and it is confined to one side of the head. Sedgwick (1863, p. 457) describes a line of descent in three generations with rudimentary ear lobes adherent to the head. The condition appears to have occurred only in the women. It was present in the grandmother, in two of her daughters, the third not being examined, and one of the two sons examined being normal. One of the daughters who had the peculiarity transmitted it to her two daughters, the son being normal. Potter (1937) describes a malformation in which the pinna is small, deformed and cup-shaped (Fig. 87). In a family with twenty-three cases in five generations both ears were always affected, the internal ear being normal. The condition was a strict dominant, DR × RR sibships numbering 22 affected : 23 normal.

Among 108,744 children admitted to the Boston Children's Hospital in twenty years, only 46 were treated for malformations of the external ear, and of these only 21 (16♂ 5♀) had *lop ears* or *bat ears* projecting from the head (MacCollum, 1938). As the condition is always bilateral and congenital, it is evidently inherited, being due to overgrowth of the conchal cartilage and lack of formation of antihelix and fossa. All but two of the cases were of Irish extraction. This is a much higher proportion than the Irish in the population, so this gene must be more frequent in the Irish people.

Among 7814 skulls of various races, but mainly Indian and Eskimo, Hrdlička (1935) made a study of *ear exostoses*. They were generally bilateral, but more frequent in the left than the right ear, more frequent in males than females. He concluded that they were localized abnormal outgrowths from the tympanic (occasionally the squamous) portion of the bony meatus. They would presumably affect the form of the external ear, and since they are generally bilateral they must have a constitutional basis. Hrdlička (1933) also described seven prehistoric skulls, five from Peru (Inca), one from Arkansas and one from New Mexico, in which the external auditory meatus was absent on the right side only. This must be a germinal defect. Some Inca skulls showed marked diminution in the lumen of the canal. The otological literature showed only 50 cases of atresia of the external bony meatus. In 10 cases both ears were affected, and 41 cases were unilateral (22 right, 9 left, 10 unstated). Stewart (1933) compared the skulls of Eskimos, Aleuts and California Indians as regards the meatus and the tympanic plate. A thick plate with resulting changes in the meatus is a hereditary feature of the Eskimo skull.

Lynch (1921) described a mutation in the house-mouse, in which the ears are about half the normal length and somewhat narrower. They differ from the normal in outline and are held close to the head, the condition being a simple recessive. Hound-ear is a variable condition in mice (McPheters and Little, 1933) and a very similar condition combined with skull defects occurs in swine. The short-ear gene in mice has recently been shown to be pleiotropic in its effects (Green and Green, 1942), producing also smaller body size, malformation of the xiphisternum and possibly neuromuscular kinkiness of the tail. Strains differ slightly in the time of gestation at which abnormal development begins to appear. There is a failure of supply of necessary substances for cartilage formation to ear and xiphisternum at a critical stage of development. Hopf (1909) records many developmental abnormalities in man and animals and describes a litter of rabbits which contained one with a single ear. From it a race of one-eared rabbits was produced.

Ritzman (1921) found that short, thick ears in a breed of sheep is a heterozygous condition, giving equal numbers of both types of offspring in crosses with the normal (sixteen short ear : sixteen long ear). The mating together of short-eared individuals produced an earless ram, which therefore clearly represents the pure recessive condition. Similar results have been independently obtained in Norway by Wriedt (1925), who adds that an earless ram mated with normal sheep gave five offspring with short ears, while an earless sheep mated with a normal ram produced one lamb with short ears. Short ear × short ear gave 2 short : 2 earless, and earless individuals mated together gave earless offspring. A simple Mendelian pair is involved, with short ear as the heterozygous condition. Short ears in sheep were said to be very common formerly in Norway, and are still found in many parts of the country.

Wassin (1929) showed similar conditions in the Karakul sheep of Bokhara with long, hanging ears. The heterozygotes (**Aa**) had shorter, more pointed ears, while in **aa** homozygotes there were no external ears. The same conditions were found in sheep in Afghanistan and goats in southern Russia. This gene in sheep probably originated in southern Turkestan. It is frequent in the Caucasus and still more so in central Asia, whence it was probably taken to Norway and America. Other recessive genes in these sheep are (1) an outgrowth of skin on the ear, (2) a long comb-like projection on the ear. Lush (1930) obtained similar results. A Tamworth sow in New Zealand (Annett, 1938) had, by a particular boar, a litter of ten pigs, four of which had their ears bilobed almost to the base. They also had cleft palate. Three were born dead and the fourth, which had deformed hind quarters, soon died. This was presumably a recessive gene.

Yamane (1915) described the inheritance of "notched ears" in Ayrshire cattle. The full notch is dominant, the heterozygous condition being usually slightly notched. Lush (1922) described the same notch in the ear in Jersey cattle. This character was found in a Jersey bull at the Texas Agricultural Experiment Station, and is inherited as a simple dominant, the bull (Gamboge's Raleigh) being heterozygous. Thirty of his calves were examined and twelve found to be without the notch. There is much variation in the degree of expression of the notch. A double human ear lobe was described by Schofield (1917). In this family the condition has been transmitted through four generations, only the right ear having the peculiarity. The accompanying chart (Fig. 91) shows its incidence. One generation or even two may be skipped, and the condition varies considerably in different individuals. Thus, in A there is a very marked deep cleft of considerable length, while in those marked B the cleft is not so well marked. In BB it was only a furrow, while in B_1 and B_2 there is a deficiency of hearing in the bilobed ear. I have seen a case in which the ear lobe was divided in an anteroposterior direction, the split extending up the back of the ear. It was regarded as a family mark.

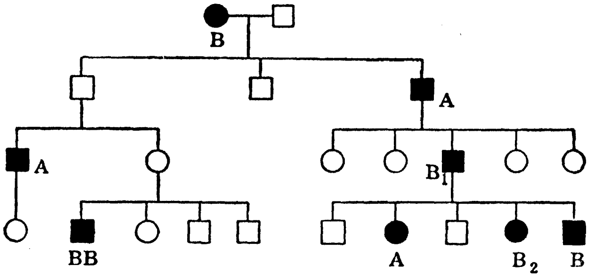

Fig. 91. Pedigree of right bilobed ear. (After Schofield)

Cervical auricles are a case of homoeosis rather than defective development. A very imperfect pinna with skin, cartilage, muscle fibres and nerves developed on the neck. The Greeks and Romans represented them on the necks of fauns and satyrs. They are rare in cattle and deer, but Lush (1924) found "double ear" dominant in Brahma cattle. Cervical auricles are always present in some breeds of goat, some breeds of sheep (Karakul, Indian, Senegal) and certain breeds of pigs have them. They are generally irregularly dominant in inheritance. In man, Cockayne (1933) found only four pedigrees, including an extensive Jewish family with two cases. It is probably a conditioned dominant, a second independent gene being perhaps required.

A Swedish girl with a natural pit in each ear lobe was described by Jenks (1916). It occurs in about the position where ears are pierced for earrings and was ascribed to this custom, as the Swedish ancestors of both sexes for many generations wore earrings. It took the form of a depression on each face of the lobe. When she was born they actually met and formed a hole, so that when she was two weeks old the doctor asked her mother why she had had the baby's ears pierced so soon. Windle (1891) states that a fissure sometimes occurs in the sulcus intertragicus of the ear, as an arrest of development. Swiecicki (1890) cites five other cases. This hole in the ear lobe was probably of similar nature. Bland-Sutton in 1890 refuted the idea that it was a case of inheritance of an acquired character. Edmonds and Keeler (1940) describe two pedigrees of this condition (Fig. 92), one of which is shown in Fig. 93. This Italian family has 9 cases (4♂ 5♀) in three generations, five of them being on the right side only and four on both sides, inheritance dominant. The typical form is a pit about 1 mm. deep in the middle of the ear lobe on both sides but not communicating. In a Russian pedigree they describe six cases in two families of the third generation, the mark in the ear lobe being combined with other ear defects. In this family the condition is either recessive or a dominant with

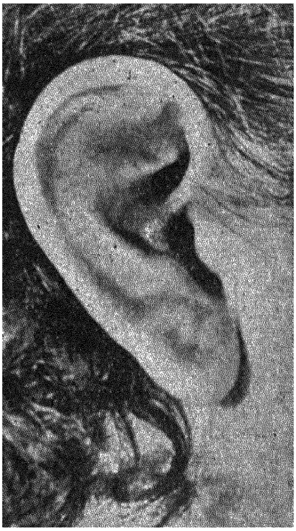

Fig. 92. Ear lobe with a depression. (After Edmonds and Keeler) (From the *J. of Heredity*)

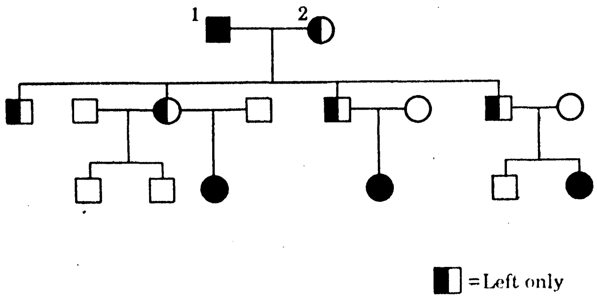

Fig. 93. Pedigree of a pit in the ear lobe. (Modified after Edmonds and Keeler)

low penetrance. The ear pits usually described are just in front of the ear and at the top (Fig. 94). They result from failure to fuse of two of the embryonic tubercles which unite to form the ear.

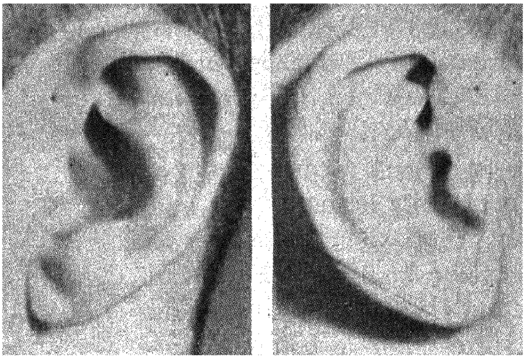

Fig. 94. Left and right ears of one man, showing pit in front of upper ear. (After Whitney) (From the *J. of Heredity*)

Kindred (1922) described a family (Fig. 95) in which the pit occurred only in the left ear. There were 10 cases (7♂ 3♀) in four generations, the inheritance dominant but with two skips. We have no satisfactory picture of the mechanism of a fixed unilateral inheritance, but as many abnormalities occur more frequently on the left than the right side there appears to be a difference in the strength of the tendency to their occurrence on the two sides. Perhaps this is due to faster growth and a higher metabolic rate on one side, as Newman suggests. Starkenstein (1928) reported two large families with regular dominant inheritance. In Whitney's (1939) case there were seven affected in three generations and the pit was frequently present in both ears, inheritance dominant

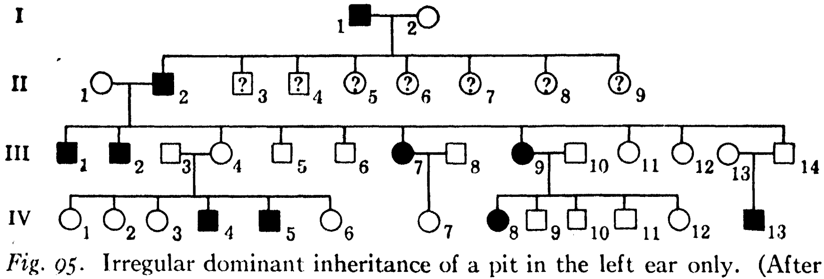

Fig. 95. Irregular dominant inheritance of a pit in the left ear only. (After Kindred)

but irregular, with a skip of at least three generations in one case. Quelprud (1940) points out that the auricle arises from the region of the left branchial cleft, being partly of mandibular and partly of hyoidal origin. His largest family has 23 cases (16♂ 7♀) in five generations, the pit occurring on either side or both, an irregular dominant. Stiles (1945) finds the pit in the ascending helix itself rather than in front of the ear. His seven pedigrees include 38 cases, mostly unilateral. In one family the condition is strictly dominant, with 9 cases (5♂ 4♀) in three generations, all but two bilateral and no skip, thus showing almost complete penetrance of the gene. In the other pedigrees the condition is more frequently unilateral and there are frequent skips indicating a penetrance of only about 52%. It seems likely that this is due to weakness of the gene rather than to modifiers. Although this condition is generally harmless, in some families suppuration (formation of pus) takes place.

A village population in Hesse showed the pit in 1.7 per cent of the people, the anomaly being present in 8 of 161 families. In a Bantu Negro population of Nyasaland, Stannus (1914) found it in 4.5 per cent of 6491 individuals examined. It was commonly unilateral, more frequent on the right side, and more frequent in females (5.2 per cent) than males (3.6 per cent). Many other congenital anomalies were present in these natives. In a twin population of 115 identical and 127 fraternal pairs it was present in 1.5 per cent. In the four pairs of identical twins in which it occurred it was present only in one member, which is not surprising, seeing that it frequently appears in only one ear. Ride (1935), from his experience at Hong Kong, finds that a pit in front of the ear occurs in 10 to 14 per cent of Asiatics.

Heusinger (1864) described two cases of branchial fistulae and figures in one a cleft on each side of the throat together with a tiny pit in front of the ear. This pit is always exactly in the position shown in Fig. 94, and it is quite independent of branchial clefts in the throat.

Heusinger collected 44 other published cases, the earliest being Dzondi, 1829, of what is now known as *fistula aüris congenita.* There may be an opening in the throat 1–15 mm. in length, which is generally regarded as a vestige of the first branchial cleft. Windle (1891) cites a pedigree of Ascherson (1832) with 8 cases of branchial fistula (1♂ 7♀) in three generations, the inheritance dominant. Cockayne (1933) published a family of Mr. E. I. Lloyd with 13 cases (6♂ 6♀) in six generations of branchial or helical fistulae or both, the inheritance dominant. Two similar families (one of them negro) are recorded. Cockayne collected 15 pedigrees of branchial or cervical fistulae with 15 affected : 19 normal in sibships, and 13♂ : ♀ 25. Pires de Lima and Monteiro (1923) described the anatomy in many cases of branchial cysts, fistulae and malformed ears. In a large number of Japanese pedigrees (Komai, 1934) fistula auris appears to be generally dominant with occasional skips. It had a frequency of 7.8 per cent in the Ryukyu Islands.

" Ear pits " result from incomplete fusion of the six auricular hillocks or tubercles which unite to form the pinna. The embryology is discussed by Quelprud (1940). It seems that branchial fistulae in the throat are quite distinct from the pre-auricular fistulae, the nature of which appears to have first been recognized by Sir James Paget in 1878. Klaber (1935) describes two cases in which a pre-auricular pit was connected with a cyst; one in a girl of six whose father's father had a larger depression in front of both ears; the other a boy of sixteen with an infected cyst in front of the pre-auricular pit on the left side. There was a small dimple in front of the right ear. Heusinger recognized inheritance in 17 of his 46 cases.

Connon (1941) describes a family with fistula auris congenita forming an ear pit. The condition is present in 10 members (4♂ 6♀) in five generations and is in the left ear in every case except one female. It is dominant, with one skip. McDonough (1941) cites the case of a pair of MZ female twins in a family which had five cases of ear pit in three generations. One twin had a pit on the left side but did not transmit it to either of her two sons; the other twin had no ear pit but nevertheless her son had it bilaterally. Such cases are a proof of the reality of failure of penetrance even when the genetic make-up and the prenatal environment were the same.

Jenkins (1928) described a family in which, instead of a pit, a congenital *skin papillus* about 4 cm. in diameter appears in front of the external meatus of the left ear. The identical condition in the same location was found in 6 cases (4♂ 2♀) in four generations of this family. It is an irregular dominant, transmitted by two men who do not show the condition.

Deafness

In man and mouse deafness can be combined with lack of equilibrium and also with hereditary movement-disturbances of head and body. Different strains of waltzing mice are "circlers" or "shakers" and they are more or less deaf. Bonnevie (1936) described a short-tailed shaker mutation with extreme movement-disturbances (associated with defective labyrinth) and blood-blebs in the dorsal median line of the head.

Deafness, like blindness, can arise from many conditions, inherited or accidental. In the latter case frequently only one ear is affected Deafness can be acquired before birth by intrauterine infection, syphilis or birth trauma. Exogenous causes include inflammation of the brain, otitis media, scarlet fever and fracture of the base of the skull in childhood. Otosclerosis is the most common cause of hereditary deafness. Some 10 per cent of ear patients have it (Fraser, 1928) (estimates range from 7 to 30 per cent) and at least 50 per cent of them give a history of deafness in the family. Estimated frequency in the population ranges from 0.5 to 0.1 per cent, females being twice as frequently affected as males. The onset is insidious, with ankylosis of the stapes to the margin of the fenestra ovalis. Changes also take place in the bony structure of the otic capsule of the temporal bone, large spaces arise in the petrosal bone, its blood vessels becoming enlarged, with other changes. A flamingo tinge is frequently visible through the transparent drumhead. The process usually begins in one ear and later involves both. The onset is usually in the twenties and thirties but may rarely be as late as seventy or as early as one year or even prenatal. In females it often begins at puberty and becomes worse at each pregnancy, so there may be some connection with sex hormones. According to Davenport, Milles and Frink (1933), the condition is essentially a localized dysostosis (failure of bone formation), which may also result from synostosis between the mastoid process and the occipital bone, or thickening of the bones around the semicircular canals or in the meatus. It is often associated with osteopsathyrosis. These authors studied sixty new families and concluded that two dominant factors, one of them sex-linked, are involved, the autosomal gene modifying the reaction of the mesenchyme while the sex-linked gene accounts for the 2 : 1 ratio of affected females to males and may affect calcium metabolism. Wittmack produced otosclerosis experimentally in hens.

Bauer and Stein (1925) collected 106 families with otosclerosis. They thought that otosclerosis and chronic progressive *labyrinthine hardness of hearing* are due to the same gene. The latter usually occurs later in life and appears to result from a defect in calcium metabolism which causes abnormal bone formation around the inner ear. There is frequently also disturbance of equilibrium, with positive Rinne tests (which indicate that the perception of tones through the air is better than through the bones of the head). In otosclerosis the Rinne test is usually negative. Labyrinthine deafness also usually shows narrowing of upper tone limits whereas otosclerosis shows narrowing of the lower tone limits. In *deaf-mutism* which results from congenital deafness or complete loss of hearing before the age of seven when the child is accustomed to speaking, the dumbness is secondary and not due to lack of organs of speech as was assumed by doctors and philosophers four hundred years ago. The organ of Corti is undeveloped, whereas in labyrinthine deafness it degenerates. In otosclerosis, unlike the other two, the auditory nerve is usually fully functional. Bauer and Stein concluded that otosclerosis depends on one or more recessive genes, but in some families two otosclerotics may have some normal children. They believe the above three forms of deafness are different aspects of the same defect, all due to similar recessive genes, often taking the form of hardness of hearing in the male and otosclerosis in the female. They found evidence of linkage between these genes and susceptibility to tuberculosis. Others have observed an asthenic hypogenital habitus in otosclerotics. Albrecht (1925a) collected ten pedigrees of labyrinthine hardness of hearing. The results are in accord with a simple dominant, 24♂ : 25♀ affected, the sibships numbering 37 affected : 36 normal. On the contrary, seven pedigrees of otosclerosis showed 20♂ : 30♀ affected, the sibships 45 affected: 40 normal. Thus they appear to be genetically distinct although clinically difficult to distinguish. Haike (1928) collected five pedigrees of otosclerosis which are probably recessive, while one is an irregular dominant with 30 cases (11♂ 19♀) in five generations. Leeson (1928) analyzed the records of over a thousand cases. In 41 per cent the onset was after thirty years. In 80 per cent the tympanic membrane was normal. Pregnancy frequently has a marked effect in accentuating the deafness.

To account for the excess of females in otosclerosis, Davenport, Milles and Frink (1933), who studied sixty new families, proposed two dominant factors, one of which was sex-linked. They separated four types of families: (1) both parents affected, (2) mother only affected, (3) father only affected, (4) both parents normal; and confirmed that whereas other types of hardness of hearing affected both sexes equally, in otosclerosis the ratio was 2♀ : 1♂. When both parents are affected, nearly all the daughters and about two-thirds of the sons are affected. When the mother is affected the number of affected sons and daughters will be equal. When the father is affected the affected daughters are about 50 per cent more than the affected sons. When both parents are normal, equal numbers of sons and daughters will be affected. When both parents are otosclerotic, their formula will generally be ♀**XxAa** × ♂**XYAa.** When normal parents have otosclerotic children the formula will generally be ♀**Xxaa** or **xxAa** × ♂**xYAa.** The results of these and other crosses can easily be worked out and were found to be in accord with the actual data, the method of inheritance being similar to that of goitre. Since half the affected females will receive an affected X from the egg and half from the sperm, whereas males will receive an affected X only from their mother, there will be twice as many female as male zygotes carrying an affected X-chromosome. These data need to be checked by the method of Czik and Mather (1938).

Dean and Bunch (1923) made a study of the auditory acuity of three brothers with an *affected auditory nerve* in a family of seven. The parents were normal and unrelated, and the deafness, which was slight at first, slowly progressed. In another family hereditary neurolabyrinthitis was present in two children, their mother and grandmother. It is found that pellagra can also produce neurolabyrinthitis. Macfarlan (1927) made a study of the hearing in a pair of middle-aged women MZ twins. They act, dress and think alike. Each had two moles on the face, identical in size and position. Their hearing rises and falls across the pitch range in almost exact correspondence. Progressive deafness was observed by Shambaugh and Shambaugh (1933) in two pairs of identical twins, one (female) aged thirty-one, the other (male) sixty-nine years old. Both pairs gave the functional reactions of *primary nerve deafness*, the latter showing a bilateral slow onset at sixty. Other members of their family showed similar deafness, so that the deafness in all four was clearly conditioned by heredity.

Rodin (1933) describes identical hearing defect in a pair of female MZ twins who had scarlet fever at six, following which the hearing began to decline. At fifteen they showed marked deafness, with audiograms that were practically identical. Such results show that the organ of Corti is like a harp whose tones are determined partly by the quality of its various strings (heredity) and partly by the nature of the forces playing upon it. Bunch (1934) used audiometer tests to show marked bilateral loss of auditory acuity in four sisters in a family of five with normal parents and no known deafness in the ancestors. The auditory fields were similar, the condition being incipient otosclerosis. Popov (1935) described a Russian family with dominant hereditary *atrophy of the acoustic* (*8th*) *nerve*, 11 cases (6♂ 5♀) in three generations.

Astel (1933) published a pedigree of otosclerosis with 13 cases (7♂ 6♀) in five generations, the sibships numbering 11 affected : 13 normal. The gene is strictly dominant with no skip. Chumlea's (1942) family is also dominant, with 9 cases (5♂ 4♀) in four generations and no skip. Soft, spongy bone replaced the bony labyrinth of the middle and inner ear. Kabat (1943) describes another family with strictly dominant otosclerosis, 19 cases (12♂ 7♀) in four generations. He thinks Davenport's pedigrees can be explained by a dominant gene with lack of penetrance. This does not account for the excess of affected females, and it is more likely that there are two different types of inheritance.

Smith (1939) described a family in which *one ear* was stone deaf, the affected ear being interchangeable (four were left, four right, and there was no relation to handedness). The gene was dominant, with

12 cases (5♂ 7♀) in four generations, three of them deaf-mutes, i.e., bilaterally affected, and one skip (Fig. 96). The labyrinth was apparently normal, the lesion being confined to the cochlea. Case II. 2 was deaf-and-dumb following measles. She married another deaf-mute and their normal son transmitted the condition to a grandson.

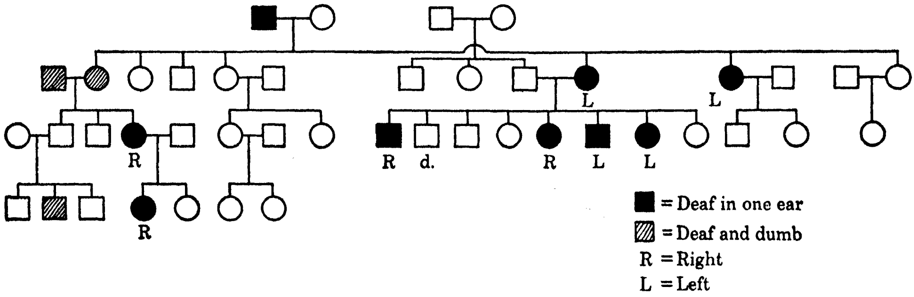

Fig. 96. Pedigree of dominant unilateral deafness. (After Smith)

Dow and Poynter (1930) described a remarkable family of capable farmers in the Ozark region of Missouri with eighteen cases of deafness (all males) in four generations, the inheritance being that of a sex-linked recessive. According to Tinkle (1933) they were deaf-mutes. Normal mothers transmitted to half their sons. Four deaf sons married unrelated deaf women whom they met at a school for the deaf. All their children and grandchildren (14♂ 11♀) are normal (the wives no doubt having a different form of deafness) but the condition will probably appear in the next generation. Of the entire family of 157 members, 10.6 per cent were deaf.

There is a strong indication that the autosomal gene for otosclerosis is in the same chromosome as the blood groups, and there should be no difficulty in testing this possible linkage. Jannuzzi (1929) found that in five different families the affected members (total fifteen) all belonged to the same blood group, but that the blood group differed from one family to another. Goekoop (1932) describes three sisters with the same fibro-angioma (a tumor containing fibres and blood vessels) of the petrous portion of the temporal bone and the middle ear, originating in the region of the Eustachian tube and no doubt determined by heredity. There were four normal sibs.

Albrecht (1926) discusses the inheritance of many forms of deafness. *Ménière's disease* is an inflammatory congestion of the semicircular canals, producing pallor, vertigo and aural and ocular disturbances and often called labyrinthine migraine. It is a relatively rare hereditary affection of the inner ear, probably caused by a defect of the vestibularis nerve. Hallpike and Cairns (1938) describe the pathological changes in two cases of Ménière's disease. The acoustic and equilibrial disturbances show certain peculiarities in the mode of onset, type and degree, and in their course during a period of years. They find that this labyrinthine disorder is due to infection in some cases. *Otitis media* or inflammation of the middle ear is a common condition in which the hereditary element is difficult to evaluate. It probably depends on susceptibility of the mucous membrane of the middle ear. Observations on monozygotic twins lend support to heredity, but it is difficult to say in what form the tendency to inflammation is transmitted from parents to children.

Lundborg (1920) concludes that hereditary *deaf-mutism* is due to one Mendelian recessive factor, and rejects Plate's hypothesis of two factors. Acquired deaf-mutism may be either intra- or extra-uterine in origin. Hence congenital deafness is not always hereditary. Irish statistics of the year 1891 register congenital deaf-mutism as 76 per cent of all cases. In Norway (1897) the number was estimated by Uchermann (1897) at 50.9 per cent, in Sweden (1904) at 40.8 per cent, and in the Malmöhus district of Sweden (1919) at only 28.2 per cent (108 in 383). Government statistics of deaf-mutes (Washington, 1920) show that they are more frequent in Negroes than in any other race in the United States.

Meningitis and scarlatina are said to be the most common causes of acquired deaf-mutism. In addition to the difficulty in distinguishing between genotypical (inherited) and phenotypical (acquired) deaf-mutism a statistical error is introduced by the fact that in small families the children may all be normals, even when the parents are heterozygous for the condition. Since these children are not added to the offspring of matings of heterozygotes, the result is more than 25 per cent of abnormals. This can be corrected by applying the formula of Weinberg, and it then closely approximates to the expected 25 per cent.

From Fay's evidence of marriages of the deaf in America (1898), 22 families had 4 to 9 children each, all deaf. The children numbered 112. Hence it appears that some genotypical deaf-mutes will have only deaf-mute children, and from this and other evidence it appears that the character is a simple recessive. The difficulty in all statistics on this subject is to distinguish between genotypic and phenotypic deaf-mutism. Love (1920) also reaches the conclusion that sporadic congenital deafness is inherited as a recessive, from a study of an Ayrshire family which has branches in America and Australia. This family shows five affected generations descended from a common ancestor three generations further back. Horne (1909), in a study of deaf-mutism, says that the number of deaf-mutes in Europe is estimated at about 1 in 1350 of the population. In England the frequency (from statistics of 1908) is 1 in 2043, Scotland 1 in 1860, Ireland 1 in 1398. Seven pedigrees are recorded, but there is no separation of hereditary and acquired cases.

Kraatz (1925), from a study of several pedigrees of hereditary deafness due to deaf-mutism and otosclerosis and from the data of Fay (1898), where the records of 4471 marriages of the deaf, with 6782 children, are given, concludes that deaf-mutism cannot be due to a single dominant, recessive or sex-linked factor, but that all the statistics except a few irregular ratios fit the theory of two recessive factors. However, lack of penetrance is a more probable explanation than two factors. As expected on the basis of two factors, deaf × deaf may give all normal children in some families. Manson (1928) gives two short pedigrees with five and three cases respectively in three generations, and the results, so far as they go, are in accord with this tentative hypothesis.

Dahlberg (1931) made a further statistical analysis of Fay's extensive material. Intermarriages of the congenitally deaf produced 683 children, of whom 29.4 ± 1.74 per cent were deaf-mutes. He concludes that they are produced not only by a single recessive factor in some families, but that at least three different dominant factors are concerned. That different recessive genes are concerned is shown by the pedigree of Mühlmann (1929). A cousin marriage and an uncle-niece marriage each produced a (recessive) deaf-mute, but when these two married they had two normal sons. If the gene were the same in both families the children would all have been deaf-mutes. There are thus probably several different biotypes of hereditary deaf-mutism.

Albrecht (1925b) points out the impossibility of determining the method of inheritance from purely statistical data, and classifies deaf-mutism into six types due to different causes, some types of the defect being inherited and some not.

Graham Bell (1884) pointed out the dangers of intermarriage of deaf-mutes, so that deafness was the first trait to be studied from a eugenical point of view. Tinkle (1933) concludes that the inheritance of otosclerosis can be accounted for by a single pair of recessive genes. He would presumably account for the excess of affected females by the assumption that the female sex hormones render the ear more susceptible, but this does not appear to be an adequate explanation of the genetical conditions. Tinkle agrees with Kraatz that deaf-mutism results from the presence of two different recessive genes. Snyder suggested that the two genes, **d** and **e**, might represent low-hearing and high-hearing respectively, but audiometer tests showed this not to be the case. Evidence from autopsies suggests rather that one gene controls development of the ectodermal part of the cochlea, the other, the auditory nerve and its ganglion. Persons who are heterozygous for "deafness" can hear perfectly on the audiometer, so the condition is recessive. Tinkle suggests that a third pair of genes controls the development of the middle and outer ear. He listed thirty-one families in Ohio in which both parents were deaf. They had eighty-nine children, 70.8 per cent of whom were deaf.

Up to 1840, the vast majority of deaf-mutes were uneducated and unmarried. Now they are educated in special schools and usually marry deaf partners. This is probably a better course than marrying into a hearing family and so spreading the genes for deafness. Definite advice regarding the sterilization of deaf-mutes will only be possible when more is known regarding the genetics of these conditions. The Volta Bureau in Washington is a clearing-house for work on deafness and further investigations are urgently needed. That sterilization in some cases is desirable is indicated by the fact that a School for the Deaf in Pennsylvania is now educating the grandchildren of some of its former pupils. Alexander Graham Bell's warning has come true.

Switzerland has the highest incidence of deaf-mutism in the world and Albrecht (1934) and Hanhart (1938) have made some of the best studies of deaf-mutism and its inheritance. The frequency of deaf-mutes is 0.12 per cent in Switzerland against 0.023 per cent in Germany, or five times as high. Another estimate gives 45,000 deaf-mutes in Germany, one-third of them hereditary. In Swiss villages where there is inbreeding the rate may be 2 per cent or more. One village of 2200 population had 44 deaf-mutes. Hanhart estimates that the latent carriers in Switzerland number over 100,000, or 1 in 40 of the population. He concluded that some 60 per cent of the deafness in Switzerland was "sporadic," many cases being deaf through cretinism. In Sweden, where there are few cretins, the ratio of congenital to acquired deafness is estimated at 100 : 67. Observations of Murray and Wilson (1945) show an association between deaf-mutism and goitre and cretinism. In three goitrous districts of Oxfordshire with a low iodine content in the soil water there were 28 deaf-mutes in a population of 36,635. In three non-goitrous areas there were only 5 deaf-mutes in 38,910. Some of the deaf-mutes have an enlarged thyroid and belong to goitrous families, but unlike goitre, both sexes are equally affected. Statistics of congenital deaf-mutism in Scotland (*Brit. Med. J.* ii. 437. 1945) show that 781 were born in the period 1918–37. They are most frequent in the north, north-east and the extreme south-west.

A remarkable pedigree of simple recessive deafness compiled by

Hanhart is the Obwaldner family, which has been traced back through eight generations from 1918 to a single couple who married in 1641. All the descendants were normal, but with considerable intermarriage, until in the last generation six different marriages (four of which were clearly intermarriages) almost simultaneously produced 9 cases of deafness (8 ♂ 1 ♀) with 20 normal sibs. The pedigree is too intricate and extensive to reproduce here, but its most striking feature is the recessive transmission through eight (in one line, nine) generations of normal ancestors from an original pair. Hanhart assumes that the mutation originated at this point, but as they were both normal the gene that one (or both) carried may have been transmitted through any number of previous generations. Thus it required three hundred years before the intermarriages between distant cousins finally brought out the recessive condition. Albrecht (1934) traced back a similar family in Kloten, near Zürich, to 1616. In the fourth and fifth generations of descendants from a single pair and collaterals there were seven cases of deafness in three families. From two of these deaf women, who married about 1750, are descended six subsequent generations with more than 374 known persons, none of whom have been deaf-mutes. Thus out-crossing has led to the disappearance of the condition. Isolation has been absent since the beginning of the nineteenth century and the family has since spread all over eastern Switzerland and into Baden and Württemberg. The evidence shows, however, that the gene remains unimpaired for any number of generations, ready to reappear whenever it meets a similar gene. Ulrich and Corrodi-Sulzer (1941) reproduce the whole pedigree through eleven generations and quote a number of documents from the eighteenth century, bearing on the deaf-mutism in this family.

Hanhart finds another type of deaf-muteness in which there are changes in the form and structure of the ductus and sacculus. It may also be differently inherited. He finds that exceptionally labyrinthine hardness of hearing can occur so early and of such high grade that it produces dominant deaf-mutism. Such a pedigree by Müller (1936) has 11 cases (5 ♂ 6 ♀) in four generations, strictly dominant, sibships 10 affected : 9 normal. There was functional defect in the vestibular apparatus. Deafness is sometimes associated with retinitis pigmentosa and oftener with feeblemindedness, and the association is too frequent to be accidental. Many deaf-mutes are sterile and the recessive form is combined with infantilism and hypogenitalism. In one family of the Obwaldner pedigree deaf-mutism was combined with heterochromia iridis on the same side together with Horner's syndrome and strabismus.

That the condition of deaf-mutism can be produced by different genes is shown by a case of Grohmann (1939). Both the parents were deaf-and-dumb but their ancestors were normal, indicating a recessive gene in each. Their daughter was normal, so the parents must have been carrying different forms of deaf-mutism.

Kloos (1938) cites a neuropathic family in which the mother and mother's mother had Huntington's chorea; the mother's sister and the father's mother were hard of hearing. Of their eleven children, three were deaf-mutes, two feebleminded and six normal. Heterozygous hardness of hearing produced (recessive) homozygous deaf-mutism in three children. The Huntington's chorea in Germany seems more variable than in the American families.

Mende (1926) described a family in which the father had white hairs in his beard but was not deaf. His five children were all deaf-mutes. Two of these had children by other deaf-mutes, but only one in six were mute. The five children also had pigmentary anomalies, white patches on hair and skin as well as pigmentation of the neck, back, arms, hands and feet (not the piebald pattern) with much persistent lanugo on their backs, and mongoloid features. There were 19 deaf-mutes (9♂ 8♀) in four generations and 8 cases (6 of them deaf-mutes) of pigmentary anomaly. The latter appears to be dominant and the former is probably recessive as usual, with different genes for deaf-mutism in the spouses. A similar Hungarian family is cited, with lack of pigmentation in five generations. One deaf-mute couple had four children, one deaf-mute; another such couple had two normal children.

A striking instance of hereditary deafness due to *bilateral acoustic tumors* is described by Gardner and Frazier (1930). The family, with 217 members in five generations, included 38 bilaterally deaf members, 15 of whom subsequently became blind through choking of the optic discs and secondary atrophy. The inheritance was that of a Mendelian dominant. In necropsy two were shown to have bilateral acoustic neurofibromata. The family had no case of von Recklinghausen's disease, and the gene is evidently distinct, but perhaps an allele, its effect being definitely localized, the acoustic tumors arising on the vestibular portion of the eighth nerve. The gene also showed increasing malignancy in this family. The onset of deafness was at about twenty years, but the average age at death from the disease was seventy-two years in the second generation, sixty-three years in the third, forty-two in the fourth and twenty-eight years in the fifth. This is equivalent to anticipation, and shows that the law of anticipation in some pedigrees may have a basis in fact.

Precěchtěl (1927) described a family with 15 cases (6♂ 8♀) of dominant *deficiency of hearing* in four generations. Six of the affected in two generations had branchial fistula (fistula colli) as well, independently inherited, more frequent on the right side and always on the right when unilateral. This is an anomaly of the second branchial cleft, whereas the first branchial cleft, which includes the middle ear and adnexes, is associated with some forms of deafness. Paget's case also combined anomalies of the first and second clefts.

It has long been known that pure white cats with blue or blue-gray eyes are invariably deaf. Sichel (1847) observed, however, that if the iris had even a spot of yellow pigment the hearing was normal. A cat whose eyes darkened at four months began to hear at the same time. Darwin (*Animals and Plants under Domestication*) observed that kittens are deaf during the first nine days when their eyes are closed. Bamber (1933) discussed these relationships and concluded that blue eyes and deafness are intimately associated with dominant white in both sexes. The cause of this correlation is still unknown, but all three conditions may be the pleiomorphic effects of one gene. Wolff (1942) shows that in such cats the organ of Corti is absent, as well as spiral ganglion cells. The deafness of white cats with blue eyes is therefore, as Darwin said, due to a slight arrest of development of the nervous system connected with the sense organs.

Hughson, Ciocco and Palmer (1939) made audiograms for air conduction and bone conduction of about 460 pupils in the Pennsylvania School for the Deaf. Complete lack of hearing ability was rare. Ninety-five per cent responded to at least one tonal frequency by air conduction in one ear, and 85 per cent in both ears. In the great majority of these children the deafness was bilateral, acquired before the age of six years and about equal in both ears, and there was no relation to sex. Fifty-four per cent were stated to be born deaf. Meningitis, trauma of the head, measles, otitis media and scarlet fever were stated to produce about half the cases, meningitis alone accounting for 17 per cent. No relation was found between auditory thresholds and the stated cause of deafness. Ciocco, Hughson and Palmer (1939) found that the auditory acuity of forty pairs of siblings differed significantly less than in forty pairs of unrelated children.

Adachi (1937) finds that the stickiness or dryness of *ear-wax* as well as the odor of axillary perspiration are racial characters. Mongoloids have dry ear-wax with little or no odor, while axil (arm-pit) odor and sticky ear-wax are inherited as a dominant in the Japanese. This condition is found in 100 per cent Negroes and Ainu, in 50 per cent of Ainu × Japanese. It is present in over 70 per cent of Europeans, 53 per cent of Micronesians, 50 per cent of Formosans, 10 per cent of Japanese, 3 per cent of Chinese, but not in Tungus or Kalmucks. Both ear and axillary secretion are connected with the sweat glands, which are more numerous in the arm-pits of those who have axillary odor. The dominant gene, **A**, is not related to skin color and is not linked to the blood groups. Burton (1865), in reference to the Dahoman Negro tribes of West Africa and their crosses with Mohammedanized tribes in Africa, says "The earliest distinction between the negro and negroid consisted not in external features but in smell. That was the best test, and the difference was occasioned by a different development of the sebaceous glands."

Lüscher (1940), using a method of examining the *tympanum* microscopically *in vivo*, compared MZ twins and concluded that the character of the tympanum is determined by heredity even in its finest details. In a further study (1944) using an ear microscope which magnified 10–20 diameters, he compared the tympanum in 9 pairs of MZ and 9 of DZ twins. He finds that normal tympana comprise a series of well defined heritable types. No two persons have the same eardrum pattern. The differences, relating partly to the epithelium but mainly to the mesodermal middle layer, are said to be as characteristic as the finger prints. In DZ twins the eardrums generally belong to the same types, whereas in MZ twins they agree also in the smaller details. Thirteen character differences were used in this study. The mucous membrane of the middle ear may be defective or may show little resistance to infections. A pair of MZ twins showed hereditary degeneration of the ear drum.

LITERATURE

Adachi, B. 1937. Das Ohrenschmalz als Rassenmerkmal und der Rassengeruch ("Achselgeruch") nebst dem Rassenunterschied der Schweissdrüsen. *Zeits. f. Rassenk.* 6:273–307. Figs. 6.

Albrecht, W. 1925a. Zur Vererbung der konstitutionell sporadischen Taubstummheit. *Arch. f. Ohrenhlk.* 112:286–291.

———. 1925b. Zur Vererbung der Otosklerose, der labyrinthären Schwerhörigkeit und konstitutionell sporadischen Taubstummheit. *Zeits. f. Mensch. Vererb. u. Konst.* 11:762–775.

———. 1926. Vererbung in der Ohrenheilkunde. *Klin. Wochens.* 5:1161–1163.

———. 1934. Die erblichen Ohrleiden und das Gesetz zur Verhütung erbkranken Nachwuchses. *Zeits. f. Hals-, Ohren- u. Nasenhlk.* 36:262–276.

Annett, H. E. 1938. A new ear defect in pigs. *J. Hered.* 29:469–470. Figs. 2.

Astel, K. 1933. Ein Stammbaum über Otosklerose. *Arch. f. Rass. u. Ges.-Biol.* 27:325–328.

Bamber, Ruth C. 1933. Correlation between white coat colour, blue eyes and deafness in cats. *J. Genet.* 27:407–413.

Bauer, J. & Stein, C. 1925. Vererbung und Konstitution bei Ohrenkrankheiten. *Zeits. f. Mensch. Vererb. u. Konst.* 10:483–545.

Bean, R. B. 1909. Filipino ears, a classification of ear types. *Phillip. J. Sci.* 4:27–53. Pls. 10, figs. 17.

Bean, R. B. 1915. Some characteristics of the external ear of American Whites, American Indians, American Negroes, Alaskan Eskimos, and Filipinos. *Am. J. Anat.* 18:201–225. Pls. 3.

Bell, A. G. 1884. Upon the formation of a deaf variety of the human race. *Nat. Acad. Sci.* 4th Memoir.

Bonnevie, K. 1936. Abortive differentiation of the ear vesicles following a hereditary brain-anomaly in the "short-tailed waltzing mice." *Genetica* Suppt. 18:105–125. Pls. 3, figs. 12.

Bunch, C. C. 1934. Familial deafness: a possible example. *Laryngoscope* 44:291–298.

Burton, R. 1865. Notes on the Dahoman. *J. Anthrop. Soc.* 1:308–321, 3:vi–xi. In Selected Papers on Anthropology, Travel and Exploration. By Sir Richard Burton. Edited by N. M. Penzer. London, 1924.

Chumlea, B. J. 1942. A pedigree of otosclerosis. *J. Hered.* 33:98–99.

Ciocco, A., Hughson, W. and Palmer, C. 1939. Resemblances in the auditory acuity of siblings. *Human Biol.* 11:259–268.

Connon, F. E. 1941. The inheritance of ear pits in six generations of a family. *J. Hered.* 32:413–414.

Dahlberg, G. 1931. Eine statistische Untersuchung über die Vererbung der Taubstummheit. *Zeits. Mensch. Vererb. u. Konst.* 15:492–517.

Davenport, C. B., Milles, B. L. & Frink, L. B. 1933. The genetic factor in otosclerosis. *Arch. of Otolaryng.* 17:135–170, 340–383.

Dean, J. W. & Bunch, C. C. 1923. A study of the tonal ranges in lesions of the acoustic nerve and its end organ. *Laryngoscope* 33:309–327.

Dow, G. S. & Poynter, C. I. 1930. The Dar family. *Eugen. News* 15:128–130.

Edmonds, H. W. & Keeler, C. E. 1940. Natural "ear-ring" holes. *J. Hered.* 31:507–510. Figs. 2.

Fay, E. A. 1898. *Marriages of the Deaf in America.* Washington. Pp. 527.

Fraser, J. S. 1928. A national investigation of otosclerosis. *Proc. Roy. Soc. Med.* 21:387–391.

Gardner, W. J. & Frazier, C. H. 1930. Bilateral acoustic neurofibromas. *Arch. of Neur. & Psychiat.* 23:266–302. Figs. 21.

Geyer, E. 1928. Vererbungsstudien am menschlichen Ohr. *Mitteil. Anthrop. Ges. Wien.* 58:6–8.

Goekoop, C. 1932. Fibro-haemangiom des Felsenbeines und des Mittelohres bei drei Schwestern. *Acta Oto-laryng.* 18:153–162. Figs. 4.

Green, E. L. & Green, M. C. 1942. The development of three manifestations of the short ear gene in the mouse. *J. Morph.* 70:1–19. Pls. 3, figs. 5.

*Grohmann, H. 1939. Heterogenie der recessiven Taubstummheit. *Der Erbarzt* 7:12–20.

Haike, H. 1928. Zum Erbgang der Otosklerose. *Arch. Rass. u. Ges.-Biol.* 20:155–169.

———. 1930. In Brugsch and Lewy, "*Biologie der Person.*" 3:577–647. Figs. 33.

Hallpike, C. S. & Cairns, H. 1938. Observations on the pathology of Ménière's syndrome. *Proc. Roy. Soc. Med.* 31:1317–1336. Figs. 29.

Hanhart, E. 1938. Die "sporadische" Taubstummheit als Prototyp einer einfach-recessiven Mutation. *Zeits. Mensch. Vererb. u. Konst.* 21:609–671. Figs. 14.

Heusinger. 1864. Hals-Kiemen-Fisteln von noch nicht beobachteter Form. *Virchow's Arch.* 29:358–380. Pl. 1.

Hildén, K. 1922. Über die Form des Ohrläppchens beim Menschen und ihre Abhängigkeit von Erbanlagen. *Hereditas* 3:351–357. Figs. 3.

———. 1929. Studien über das Vorkommen der Darwinschen Ohrspitze in der Bevölkerung Finnlands. *Fennia* 52: No. 4, pp. 39.

Hopf, L. 1909. *The Human Species.* London.

Horne, J. 1909. Deaf-mutism. *Treas. Human Inher.* Pp. 27–29, 69–72, 124–126, pls. 4.

Hrdlička, A. 1933. Seven prehistoric American skulls with complete absence of external auditory meatus. *Am. J. Phys. Anthrop.* 17:355–377. Pls. 6.

———. 1935. Ear exostoses. *Smithsonian Misc. Coll.* 93. No. 6. Pp. 98, pls. 5.

Hughson, W., Ciocco, A. and Palmer, C. 1939. Studies of pupils of the Pennsylvania School for the Deaf. *Arch. of Otolaryng.* 29:403–416.

Jannuzzi, S. 1929. Gruppi sanguini ed otosclerosi-richerche. *Arch. ital. di Otolog.* 40:499–518.

Jenkins, R. 1928. A skin papillus in four generations. *J. Hered.* 19:174.

Jenks, A. E. 1916. Pitted ear-lobes of congenital origin. *J. Hered.* 7:553–554. Fig. 1.

Kabat, C. 1943. A family history of deafness. *J. Hered.* 34:377–378.

*Keith, A. 1906. The results of an anthropological investigation of the external ear. *Proc. Anat. & Anthrop. Soc. Aberdeen* 1904–1906: 217–239.

Kindred, J. E. 1922. Inheritance of a pit in the skin of the left ear. *J. Hered.* 12:336–337.

Klaber, R. 1935. Two cases of pre-auricular fistula. *Proc. Roy. Soc. Med.* 28:1553–1554. Figs. 2.

Kloos, G. 1938. Gehäufte erbliche Taubheit in einer Huntington-Familie. *Münch. Med. Woch.* 85:94–96.

Kraatz, J. J. 1925. Hereditary deaf-mutism. *J. Hered.* 16:265–270. Figs. 3.

Leeson, L. A. 1928. The clinical aspects of otosclerosis. *J. Laryng. & Otol.* 43:89–91.

Love, J. K. 1920. The origin of sporadic congenital deafness. *J. Laryng., Rhinol. & Otol.* 35:263–270.

*Lüscher, E. 1940. Erbbiologische Untersuchungen an den Trommelfellen von eineiigen Zwillingen. *Verhandl. Schweiz. Naturforsch. Ges.* 120:76–77.

———. 1944. Otomikroskopische Beobachtungen an Zwillingstrommelfellen. *Arch. J. Klaus-Stift.* 19:461–462.

Lundborg, H. 1920. Hereditary transmission of genotypical deaf-mutism. *Hereditas* 1:35–40.

Lush, J. L. 1922. An hereditary notch in the ears of Jersey cattle. *J. Hered.* 13:8–13. Figs. 9.

Lush, J. L. 1924. "Double ears" in Brahma cattle. *J. Hered.* 15:93–96. Figs. 2.

———. 1930. Earlessness in Karakul sheep. *J. Hered.* 21:107–112. Figs. 6.

Lynch, C. 1921. Short-ears, an autosomal mutation in the house-mouse. *Amer. Nat.* 55:421–426.

Macfarlan, D. 1927. Identical hearing in identical twins. *Laryngoscope* 37:846.

Manson, J. S. 1928. *Observations on Human Heredity.* Lewis: London. Pp. 84, pls. 8, figs. 19.

McDonough, E. S. 1941. On the inheritance of ear pit with special reference to twins. *J. Hered.* 32:169–170.

McPheters, B. W. & Little, C. C. 1933. Hound-eared mice. *J. Hered.* 24:157–158.

Mende, I. 1926. Über eine Familie hereditär degenerativer Taubstummer mit mongoloidem Einschlag und teilweisem Leukismus der Haut und Haare. *Arch. f. Kinderhlk.* 79:214–222. Figs. 2.

Mühlmann, W. E. 1929. Ein ungewöhnlicher Stammbaum über Taubstummheit. *Arch. f. Rass. Ges.-Biol.* 22:181–183.

Müller, E. 1936. Vestibularisstörung bei erblicher Taubheit. *Arch. Ohr-usw. Heilk.* 142:156–163.

Murray, M. M. & Wilson, D. C. 1945. Deaf-mutism and low iodine content of water. *Nature* 155:79.

Pires de Lima, J. A. & Monteiro, H. B. 1923. Aparelho branquial e suas perturbações evolutivas. *Arquiv. de Anat. e Antrop.* 8:185–238. Figs. 27.

Popov, N. A. 1935. Hereditäre Atrophie der Hörnerven. *Zeits. Hals-usw. Hlk.* 37:407–413.

Potter, Edith L. 1937. A hereditary ear malformation. *J. Hered.* 28:255–258. Figs. 3.

Powell, E. F. & Whitney, D. D. 1937. Ear lobe inheritance. *J. Hered.* 28:184–186. Figs. 2.

Precěchtěl, A. 1927. Pedigree of anomalies in the first and second branchial cleft. *Acta Otolaryng.* 11:23–30.

Quelprud, T. 1932. Untersuchungen der Ohrmuschel von Zwillingen. *Zeits. f. Abst. u. Vererb.* 62:160–165.

———. 1934a. Familienforschungen über Merkmale des äusseren Ohres. *Zeits. f. Abst. u. Vererb.* 67:296–299. Figs. 4.

———. 1934b. Zur Erblichkeit des Darwinschen Höckerchens. *Zeits. f. Morph. u. Anthr.* 34:343–363. Pl. 1.

———. 1939. Die Vererbung des Crus Cymbae der menschlichen Ohrmuschel. *Proc. Anthrop. Cong. Copenhagen.* P. 192.

———. 1940. Ear pit and its inheritance. *J. Hered.* 31:379–384. Figs. 4.

———. 1941. Variability and genetics of the human external ear. *Proc. Internat. Congr. Genetics Edinburgh.* P. 243.

Regmunt-Sobieszcyanski, L. 1933. Nowa odmiana wzgórka Darwina u ludzi uzupelniajaca klasyfikacje schwalbergo. *Folia Morph.* 4:85–89.

Ride, L. 1935. *Arch. J. Klaus-Stift.* 10:42.

Ritzman, E. G. 1921. Breeding earless sheep. *J. Hered.* 11:238–240. Figs. 4.

Rodin, F. H. 1933. Identical hearing defect in identical twins. *Arch. of Otolaryng.* 17:179–182.

Schofield, R. 1917. Inheritance of a bilobed ear. *J. Hered.* 8:517–518. Figs. 2.

Sedgwick, W. 1861. On sexual limitation in hereditary disease. *Brit. & Foreign Med.-Chir. Review* 27:477–489, 28:198–214.

———. 1863. On the influence of sex in hereditary disease. *Brit. & Foreign Med.-Chir. Review* 31:445–478, 32:159–197.

Shambaugh, G. E., Jr. & Shambaugh, G. E. 1933. Progressive deafness occurring in identical twins. *Arch. of Otolaryng.* 17:171–178.

Sichel, Dr. 1847. Note sur un rapport remarquable entre le pigment des poils et de l'iris et la faculté de l'ouie chez certains animaux. *Ann. des Sci. Nat. Zool.*, Ser. 3, 8:239–241.

Smith, A. B. 1939. Unilateral hereditary deafness. *Lancet* 237:1172–1173.

Stannus, H. S. 1914. Congenital anomalies in a native African race. *Biometrika* 10:1–24. Pls. 6.

Starkenstein, E. 1928. Ueber die Vererbung einer branchiogenen Fistel. *Med. Klin.* 24:701.

Stewart, T. D. 1933. The tympanic plate and external auditory meatus in the Eskimo. *Am. J. Phys. Anthrop.* 17:481–496.

Stiles, K. A. 1945. The inheritance of pitted ear. *J. Hered.* 36:53–61. Figs. 7.

Swiecicki, Dr. 1890. Zur ontogenetischen Bedeutung der congenitalen Fissuren des Ohrläppchens. *Arch. f. Anat. u. Physiol.* 295–299. Figs. 3.

Tinkle, W. J. 1933. Deafness as a eugenical problem. *J. Hered.* 24:13–18.

Tommasi, C. 1907. Ipertricosi auricolare famigliare. *Arch. d. Psichiatr., Neuropat., Antropol., Crim. e Med. Legale* 28:60–67. Figs. 5. See also *Giorn. di Psich. Clin. e Tech. Manic.* 35:1–21. Figs. 5.

*Uchermann. 1897. *De dövstumme i Norge.* Christiania.

Ulrich, K. & Corrodi-Sulzer, A. 1941. Sporadisch Taubstumme in der ersten Hälfte des 18. Jahrhunderts und ihre Nachkommen. *Arch. J. Klaus-Stift.* 16:559–598.

Wassin, B. 1929. Ohrlosigkeit bei Schafen und Ziegen. *Zeits. f. Abst. u. Vererb.* 49:95–104. Figs. 10.

Whitney, D. D. 1939. Three generations of ear pits. *J. Hered.* 30:323–324. Figs. 5.

Wiener, A. S. 1937. Complications in ear genetics. *J. Hered.* 28:425–426.

Windle, B. C. A. 1891. Teratological evidence as to the heredity of acquired conditions. *J. Linn. Soc., Zool.* 23:448–502.

Wolff, Dorothy. 1942. Three generations of deaf white cats. *J. Hered.* 33:39–43. Figs. 3.

Wriedt, Chr. 1925. Die Erblichkeitsverhältnisse der ohrlosen und kurzohrigen Schafe und die Verbreitung dieser Typen in Norwegen. *Zeits. f. Abst. u. Vererb.* 36:430–437. Figs. 4.

Yamane, J. 1915. On the inheritance of an aural abnormality in the Ayrshire cattle. *J. Coll. Agric. Tohoku Imp. Univ.* 6:166–170.

Chapter IX

ALBINISM

IT IS a general rule in human heredity, though not without exceptions, that the more extreme form of any mutation is recessive, the less extreme gene being dominant in inheritance. A survey of the recent work on total and partial albinism leads to the view that while total albinism is generally a recessive condition (as already known), partial albinism in the form of piebaldism, spotting, a white blaze in the forehead or other forms of *albinismus conscriptus* are dominant, but not alleles of *albinismus totalis.*

We may deal first with complete or total albinism. This condition varies, especially as regards eye pigmentation, but we may include in it all cases in which the skin color is more or less uniformly white and the hair white or cream color. These are the usual albinos. Typically the skin and eyes are pigmentless, including hair, eyebrows and eyelashes. They often show strabismus, refractive anomalies, nystagmus and photophobia, but traces of pigment are nearly always present. In albinos of the colored races the iris is less transparent and they frequently have blue eyes or even light brown. Davenport and Davenport (1910) published three families in which two albino parents produced only albino children — a total of four, and refers to another albino pair with five children, all albinos, thus confirming the recessive character of complete albinism. One of the albino mothers appeared in a Negro family, and as she had an albino child by a white albino we may conclude that the gene for albinism in the Negro is the same (and probably in the same chromosome locus) as in the white race.

Crosses between Chinese and various Malayan types in Celebes and the Philippines not infrequently produce albino children, indicating that the recessive gene for albinism in these two races is the same. Complete albinism appears to be found in all races, perhaps represented by the same gene. But the frequency of this gene varies greatly, from perhaps 7 per 1000 in the San Blas Indians of Darien to 5 per 1000 in the Hopi Indians, 1 per 10,000 in Norway, 1 in 29,000 in

Italy and 1 in 100,000 in France and Russia. This may depend on differences in the mutation frequency, but as to the causes of such differences there is no evidence at the present time. That they exist must, however, have some evolutionary significance. It supports the general view (Gates, 1936) that differences in mutation rates arise within a species or a group of related species. While total albinism is generally recessive, Cockayne (1933) finds that the recorded cases number 780 males and 629 females. The large excess of males supports the view that albinism is a sex-linked recessive in some families.

It is also found that about 20 per cent of the parents of albinos are cousins. This corresponds to a frequency in the white population of *ca.* 1 in 200,000. But as albinism is far more common than this, it follows that there are probably different recessive genes in the population. Pearson reckoned the frequency of albinos in Britain at 1 in 20,000. With random mating, 1 in 283 would then be heterozygous for the gene.

Albinism is known in most races and probably occurs in all. In Germany, out of nearly four million children dealt with, about four hundred had "white hair." This would give a frequency of 1 in 10,000. A similar proportion was found in Norway. Of the 400 only 32 had "red eyes," hence only one complete albino in 200,000, but the true prevalence may be greater. In Austria, from statistics of insane albinotics, it was estimated that 1 in 400, or 1 in 2000 of the population were albinotics. This very high estimate may be due to linkage or perhaps merely chance association between albinism and mental derangement.

In Scotland, 100 to 150 living albinos were recorded from about half the population. This indicates a frequency of 1 in every 15,000 to 25,000 inhabitants. Less satisfactory records are available from many other countries and races.

Illustrations of one albino family are given by Davenport (1916). Zimmermann (1923) described five families with twelve typical total albinos (recessive) and three families with thirty-one cases (dominant) of "albinoids." The latter differed from full albinos only in that the skin and hair were slightly more pigmented, the iris not pink and the hair not so fine. They all had weak eyes and photophobia. Thus the difference between the dominant and recessive forms can be quite small. Two sporadic cases of partial albinism were also described.

A recent careful paper by Pipkin and Pipkin (1942) describes five families of Negro albinos in Texas with a total of nineteen albino members. In three pedigrees the condition was recessive, in one (with eight cases) dominant and in one (six cases) an irregular dominant.

There was no difference in pigmentation between the dominant and recessive forms. It thus appears that total albinism can occasionally be dominant in the Negro race and nearly total albinism at least can be dominant in the white race. These authors cite several other records of albinism. In the eleven Negro albinos examined, the skin was very fair, frequently developing very marked freckles and in certain cases lesions of the skin from exposure to sunlight. The hair color varied from almost white to canary yellow to reddish, and the iris from blue to hazel to cinnamon-brown, but even those with brown eyes suffered from photophobia. The pupils were black in natural light except in one case when they were purple. All showed nystagmus, and strabismus was common. The same authors (1943) find that in the Negro family with dominant albinism a pit in front of the ear (*q.v.*) is also dominant, and there are indications of linkage between the two conditions. The kinky hair of eight of these albinos was studied (1944). It ranged in color from pale straw to yellow and reddish, but showed no unusual fineness of texture.

That albinism can also be recessive sex-linked in inheritance is shown by four pedigrees in the extensive Pearson monograph (1913). They contain a total of thirty-four cases, all males, the transmission being through their normal daughters to half the grandsons. In these families the albinism was not quite complete. In the largest family five albinos had nystagmus and five had not. The hair was nearly white to yellowish in babyhood, becoming light mouse-color in the adults. The eyes were gray-blue but showed pink because of deficient choroidal pigment. The other families were similar, but in one the albinos had myopia and astigmatism while in two other families they were hypermetropic. Evidently in all these families a gene is present which is distinct from that for ordinary recessive albinism. Thus albinism joins the list of those human characters which can be inherited in three ways — dominant, recessive and sex-linked. Hogben (1931) showed that in recessive pedigrees of albinism an excess of affected males is recorded. He suggested that possibly the gene is semilethal in the female, but not in the male. Haldane (1938) suggests that the explanation is a social one, that male albinos are more likely to be met outside their homes and thus become probands. The excess of males would be explained, however, if in some of the supposed recessive families the gene were really sex-linked.

Wlissidis (1928) described a family with four albinos (all males) having white hair and eyelashes and pink eyes, and twenty-three blonds in five generations. The parents of the albino (two families) were all dark, not blond. Blondness is inherited as a recessive to dark, except that in one family two blond parents had three blond and two dark children, and in another, a blond and an albino had one dark and three blond children. The albinos were affected with nystagmus and were myopic. There may be a greater frequency of albinism in very fair families, but albinos also arise from parents with dark brown or black hair. Possibly blond hair is genetically linked with the gene for albinism. Ebstein and Günther (1914) described a family with 6 cases of total albinism (5 ♂ 1 ♀) and seven normal sibs. The father had dark brown hair and brown eyes, the mother dark blond hair and blue eyes. A family with dominant partial albinism (ten cases in four generations) is also recorded — a white forelock and white markings on the body.

Lange (1935) described a German family with ten cases of recessive albinism in four generations, five cases of insanity, two of idiocy and four of blindness. Waardenburg (1932), in his monograph, gives an extended account of albinism with special reference to the eye. He finds that each component of the albinism syndrome can occur as a separate hereditary anomaly, i.e., lack of pigment, absence of macula lutea, nystagmus; yet a single gene with different manifestations (polyphany) is involved in total albinism. Albinism may also be confined to the eyes without affecting the hair or skin color. Gamble (1924) records several cases and one is recorded from Japan. A boy with albinotic eyes had light brown hair and normal skin color. Many albinos are myopic through a lengthening of the axis of the eye. Waardenburg (1935) finds that in some cases at least the heterozygous parents of albinos can be recognized by an abnormal transparency of the iris. He cites the case of Swab (1931), in which a white man, by incest with his daughter, whose mother was a negress, produced an albinotic idiot son.

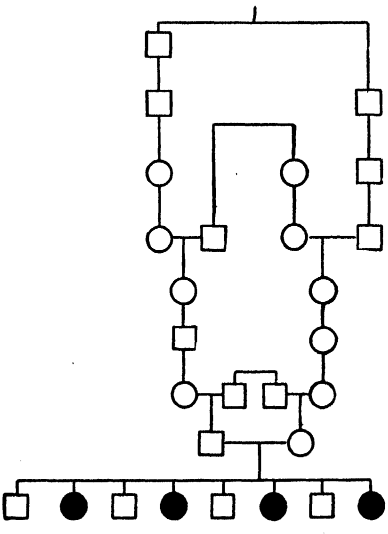

Fig. 97. Pedigree of recessive albinism. (After Sanders)

Sanders (1938) made an extensive study of albinism in Holland, collecting 140 families with 216 albinos. The ancestry was traced back in some cases ten generations, or even more, by means of the church books. A typical pedigree is shown in Fig. 97. In all cases consanguinity is present in the ancestry, with frequently repeated intermarriages. These albino families show fifteen times as many consanguineous marriages as the general population, the rate of the latter being 6.5 per 1000 marriages. Two families carrying recessive albinism had each two cases of a white lock of hair — probably a separate dominant gene, apparently not an allele.

A family in which albinism was carried as a recessive for five generations is described by Sedgwick (1861) (Fig. 98). One of the original ancestors of generation I must have been carrying albinism as a recessive. The wife of II. 1 must have been in the same condition. Their daughter (III. 1) was the only descendant of this son to show albinism.

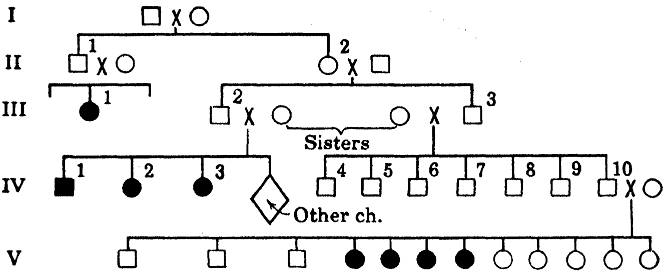

Fig. 98. Pedigree of recessive albinism. (After Sedgwick)

The two grandsons, III. 2 and III. 3, married sisters, both of whom apparently carried albinism recessive. Number III. 3 had seven normal sons, five of whom married, but only one of them had albino children. This family numbered three normal sons, and nine daughters, four of whom were albinos. The mother again must have carried albinism as well as the father, if the condition is, as usual, a strict recessive.

The term *albinoidism* or leucism has been applied to dominant albinism, which is slightly less extreme than recessive albinism. Affected individuals have photophobia but no ocular defects, the hair and skin being slightly darker but the texture of hair less fine than in pure albinos. The eyes may be blue or gray or, in Pearson's families No. 621 and 352, pink and showing nystagmus. In the latter families some members were indistinguishable from recessive albinos.

The elaborate monograph on albinism in man, by Pearson, Nettleship and Usher (1911–1913) was a detailed treatment, giving not only a fully illustrated description of the external features and the histology of the skin and eye pigmentation in albinotic individuals, but also dealing with the history of the subject. Pearson divided albinotics into six classes, but his categories are not genetic. Albinism is described in many native races and peoples.

Some of the earliest records are given by Parsons (1766). Two black Negro slaves from 300 miles inland from the Gold Coast were taken to Virginia in 1755. Their first child was an albino with white woolly hair. They afterward had two black children. A similar case of a white (albino) Negro girl from black parents was shown in London four years previously. The same author cites the following cases:

About 1746, two black slaves in Virginia had a white (albino) child. The father belonged to a family which had produced an albino child in several previous generations.

In York, a black man married a white woman and they had an "intensely black" (not "tawny" or mulatto) child. In another such marriage in London in 1747 the child was white but its right buttock and thigh were black. In another case, a boy born of black parents on the Spanish main was "mottled all over with black and white spots." Several copies of his portrait were made. The author also refers to Wafer's account of white Indians (*vide infra*).

Several cases of white-spotting in Negroes, similar to the classical types seen in paintings of the eighteenth century, have been described in modern times. Pearson (1913) contended that they arise *de novo* when a white-black cross or mixed race is crossed back with a pure white or black. Only rarely do such crosses yield a spotted type, and it now appears probable that this is due to an invisible spotting factor carried in certain white persons and determining the fairly definite pattern which usually appears. If this pattern factor is ever present in the Negro race, it should produce spotting without a previous cross, but I know of no such case. My former hypothesis of a dilution effect on the pigmentation (Gates, 1929) does not account for the definiteness of this pattern. Beginning as a blaze in the forehead, with spotting of the arms, the back and the extremities are largely black with albinotic patches in the epigastric region and often broad "garters" about the knees. In certain cases there appears to be some extension of the pigmented areas as the child develops. The Honduras piebald (Pearson, 1913) had five normal mulatto siblings. His mother combined Mexican and Negro blood, while the father was pure Negro.

An early record of pied individuals is found in a paper by J. Morgan (1786) in Philadelphia, but they were described as early as Ptolemy and Apollonius. A girl two years of age born in St. Lucia, West Indies, had a clear black skin verging to brown, except for a white spot an inch wide on the forehead, extending from the root of the nose upward into the hair, which was also white on this area but curly like that of a Negro. There was a large black spot in the middle of the forehead.

The inner half of each eyelid was white and there was a white spot on the chin. The upper and middle arms were white with black spots; the breast, abdomen, arms and thighs were mostly white. This is fairly typical of the classical piebald marking.

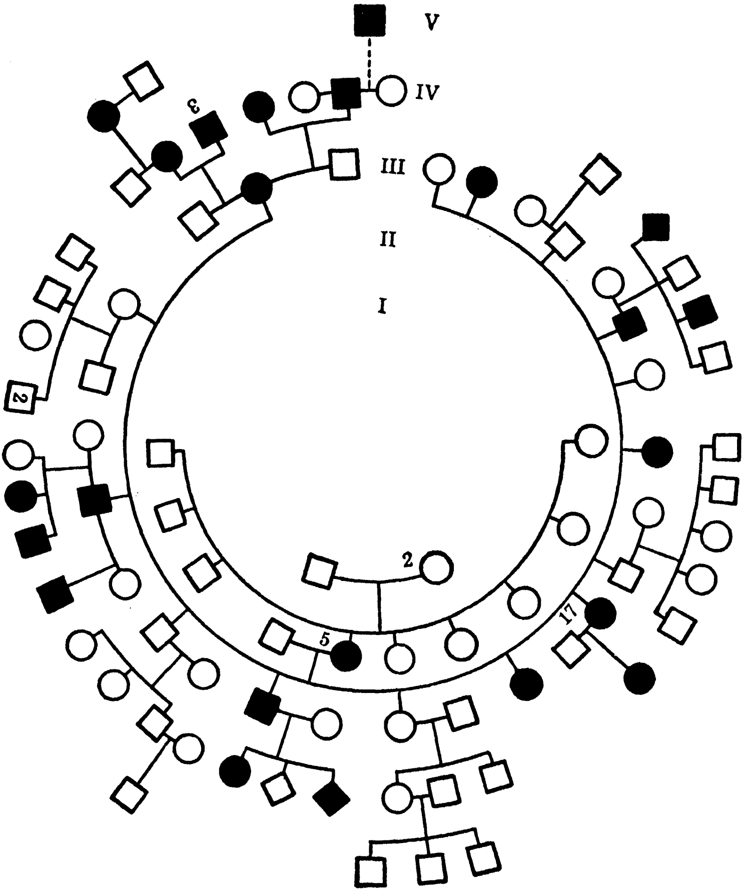

Fig. 99. Pedigree of congenital white spotting in Negroes. (After Keeler)

Another case is cited of a boy two years old born in Guadeloupe from a negress and a white man. The father had spots of deeper white on his body and the son showed the same distribution of spots. The father's mother and one brother had the same markings. This case of inheritance of a *spotting pattern* in a white family seems to explain the others.

In the case recorded by Simpson and Castle (1913), the spotting originated as a novelty — a spotted woman born from ordinary mulatto parents in Louisiana in 1853. No case of spotting had previously been known in that part of the country. She married a normal black Negro, and their children numbered fifteen, eight spotted like the mother, and seven normal, but varying in depth of color as is usual with mulattoes. Hence she was heterozygous. A fuller history of the later generations is given by Keeler (1934). The piebalds number 23 (9♂ 12♀) in four generations (Fig. 99). They travelled in exhibitions. The father of IV. 6 is an Italian. The pigmented parts of her skin are lighter than in her relatives but the pattern is very similar. The inheritance is dominant, sibships numbering 24 piebald : 11 normal, a large excess of piebalds. The condition arose in II. 5, either as a mutation or, more probably, her father was a white piebald whose latent markings were not noticeable except on a colored skin.

The piebald condition is stable; Stannus (1913) also recorded its transmission in Nyasaland for two to five generations, appearing in nine individuals is one native family.

Seligman (1902) described a Papuan family with two albino girls and a piebald boy in three generations, the inheritance recessive. The hair of the albinos was tow-colored, the skin from pink-white to café au lait, the eyes greenish, hazel or brown and there was no nystagmus. He cites other cases: Finsch saw in New Guinea a family with three cases of whitish-brown hair, blue eyes and skin color like that of Europeans. The *Challenger* expedition in Fiji saw an albino boy with white skin and pale gray eyes. The United States exploring expedition saw in Fiji in 1840 a man with "dirty white" skin marked with small brown spots, hair pigmented, eyebrows and lashes flaxen, iris blue. The same expedition saw near the Ellice Group two in a family with reddish white skin, hair flaxen, eyes light blue and large brown freckles (Nordic type). From these and other records it is clear that albinos of the colored races generally have more iris pigment than albinos of the white race. They are probably recessive in inheritance, but in the light of Zimmermann's records some of them might be dominant. They are by no means a uniform group but probably a series of alleles, some of them illustrating how the white race arose from colored ancestors. The relation of eye color to hair and skin color in albinos of different races requires much further genetic study.

Several other cases may be added. Burton (1863) described in Accra, W. Africa, a "semi-albino" with skin café-au-lait, hair yellow, short and woolly, eyes brown; and several others in Benin. Boyle (1865) writes of a native in Borneo with dirty-white skin color with large freckles, eyes pale gray and hair "of no known color." This condition was said not to be rare. The parents were normal but a brother and sister and several ancestors were albinos. Biegel (1868) described a man in London suffering from progressive muscular atrophy, whose skin became spotted with black in the pattern of negro piebalds. A latent spotting pattern was probably present. Atgier

(1910) described an albino negro from Dahomey. His relatives were all normal. His skin was rosy white, hair yellow but woolly, iris blue. He had photophobia and was very myopic, with lateral nystagmus. The author mentions a pied negro and cites (1) a black couple having four albino children, (2) another negro couple with 8 children, four albinos.

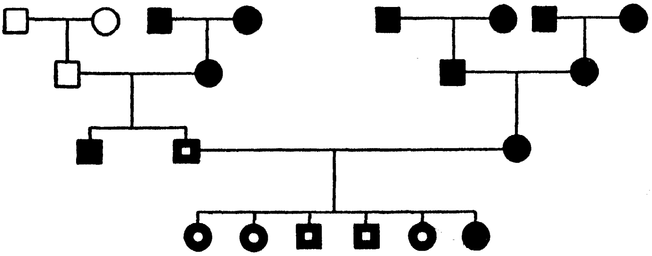

Fig. 100. Albinism inherited in crosses between French and Negroes. (After Christianson)

Christianson (1941) observed two families of complete albinos (pupils reddish and complete absence of pigment from eyes, hair and skin) in the Seychelles. They also had nystagmus, photophobia and myopia but no mental defect. In family A the father was an albino, his father being of pure French descent and his mother of Malgache stock from Madagascar (Fig. 100). The wife (III. 3) was of Negro stock from Africa. Five of their six children were albinos, from which it appears that their father's albinism, although complete, was probably dominant. The B family was of the ordinary type, with one albino in a Negro family of seven children. Many more accurate records of albinism will be required before the racial genetics of this condition can be clarified.

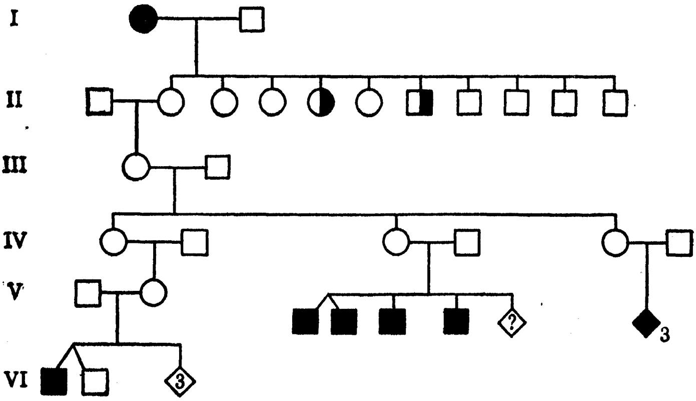

Fig. 101. Inheritance of albinism and twinning. (After Windle)

A pedigree (Fig. 101) of albinism has been constructed from statements of Windle (1935) regarding a Mexican family on Santa Catalina

Island, California. Case VI. 1 is a full albino with white hair and pinkish eyes. Case I. 1 was an albino and it is said that two of her children were albino mosaics, the girl having half her hair white and half black, with one blue eye and one black. The boy's hair is said to have been divided in the same way but both his eyes were "black." Although such mosaics are very rare, Bond (1912) recorded a case in which, in two of the nine offspring of an English woman with straight brown hair and a West African Negro, kinky hair occupied the sides of the head and the straight hair of the mother a patch on the vertex.

Pardo-Costello (1926) described a family with 11 cases (6♂ 5♀) of congenital partial albinism in four generations. The condition consists of milky white patches on the skin, irregularly distributed and often symmetrically placed, the distribution being more or less the same in all members of the family. The individuals were otherwise normal. The inheritance is that of a Mendelian dominant, but the sibs of three generations number ten affected : five normal.

In an English family the inheritance of a white forelock has been traced through six generations by Harman (1909). The white forelock is accompanied by a patch of white skin spreading like a flare down the middle of the forehead. In some members of the family there are also patches of pure white skin on the median line of the trunk or the inner sides of the calves. The eyes were normal, with no white eyelashes or parti-colored irides. The members of the family are long-lived and robust, but have a tendency to early whitening of the hair. This piebald marking was found in 24 individuals belonging to 9 childships among a total of 138 individuals in the 6 generations. The children of normals were all normal.

Pearson (1921) has since described another very similar case, with a white patch or flare on the forehead and hair. In this family there were seven affected members in four generations. This family also goes gray very early, and there is some tuberculosis but no consanguinity. This feature resembles the white "star" marking often seen in the forehead of horses and cattle, and frequently accompanied by white markings on the extremities. In this family the original great-grandmother in the pedigree must have been heterozygous. In the succeeding three generations the numbers of members which were normal or flared were 13 : 6. This is a rather wide departure from the 1 : 1 ratio expected if the trait were a simple dominant, the odds against its occurrence being 17.5 to 1, but it is not statistically significant. Since unaffected members never transmit the flare, it cannot be a regular recessive.

The occurrence and inheritance of a differently colored, usually white, patch of hair, is a fairly common phenomenon. Darwin (*Animals and Plants under Domestication*, Chap. XII) cites an English family in which "for many generations some members had a single lock differently colored from the rest of the hair," and an Irish family in which a small white lock occurred in son, mother and grandmother.

Cockayne (1914) states that piebalds are very uncommon both in black and white races. He described a piebald English family of six generations with nineteen affected members, belonging to a farming stock near Bury St. Edmunds, Suffolk. Some members of the family are fair and some dark (brunet), but both inherit the peculiarity, which consists of a blaze in the forehead. Three members of this family have heterochromidia iridis, and some have extensive white patches of skin on the body. In the last four generations of affected families the total numbers are seventeen having the flare to twelve[1] normal. This is in general accord with Pearson's case; but the excess is on the other side and is not significant in either case. Cockayne (1935) has described another piebald family from Suffolk, with 12 cases (3 ♂ 9 ♀) in four generations. They have a frontal blaze with patches on the forehead, arms and legs. Most of them have light eyes and fair hair while most of the normals have dark eyes and hair, so there is probably linkage between fair complexion and piebaldness.

A family with a white forelock occurring in four generations has been described by Holmes and Schofield (1917). This lock occurs in the centre of the fore part of the scalp, the region affected being quite small (size of a florin). Heterozygous females do not show the mark. The character is then dominant in males and recessive in females (see Fig. 102), like the inheritance of horns in crosses of a breed of sheep in which only the males have horns with one in which both sexes are hornless. It must be autosomal as fathers transmit it to sons, and it cannot be in the Y because daughters transmit it. In a white forelock family, described by Pearson, Nettleship and Usher in the monograph on albinism in man, the white lock occurred only

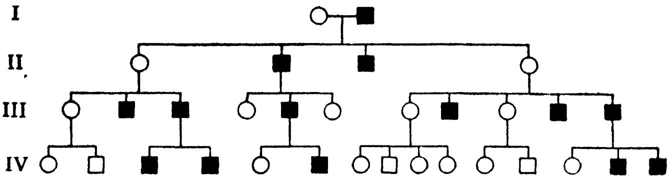

Fig. 102. White forelock dominant in males and recessive in females. (After Holmes and Schofield)

in males, but was transmitted through females, skipping a generation in each case, hence sex-linked.

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[1] One of these is doubtful.

An extensive pedigree of a white-lock family is given by Miller (1915). The condition was traced through six generations, including 203 individuals. Dr. W. B. Little, whose mother is known to have had the lock, emigrated from Carlisle, England, to New Brunswick, Canada, about 1824, and his descendants through four generations show the white lock or flare. Some members of the family also have one or more colorless spots on their bodies. The condition behaves as a simple dominant, the numbers being 51 normal : 45 with the flare. Where both parents are normal all the children are the same. This family traces its origin back through the Percys and Mortimers to Edward III. That the white lock is, at least, as old as the family of Harry (Hotspur) Percy is known by the tradition that the white lock originated in connection with his death at the battle of Shrewsbury in 1403. When the news of his death reached his wife, she is said to have swooned and to have given birth shortly afterward to a son bearing a white patch on his forehead. One member of the family has found from other records that the patch goes back at least to the Percys. It happens, also, that Lady Percy was an albino. But albinism and a white lock appear to be in separate loci, the latter much more frequent.

Meirowsky and Spickernagel (1926) described an albinotic family in which the same pattern of white patches on skin and hair could be traced through five generations and appeared as birth-marks. The inheritance was dominant.

The earliest record of an inherited white forelock is that of Rizzoli (1877), who described an Italian family with 19 cases (8♂ 11♀) in six generations. The sibships numbered 16 affected : 14 normal and the pedigree shows it to be a strict dominant without skips.

Sanders (1934) described 20 cases of white forelock combined with white spots on the breast and legs. The inheritance was strictly dominant in this family and also in two other Dutch families (Sanders, 1935), one showing 15 cases (7♂ 8♀) in six generations. From seven other papers the sibships numbered 159 spotted : 151 normal. Nussey's (1938a) piebald family was the fourth recorded in England. A blaze in the forehead is combined with unpigmented patches of skin on the forehead, stomach and legs. There were 21 cases (12♂ 9♀) in five generations — a strict dominant. Nussey (1938b) also records a probable mutation of white forelock (Fig. 103) in a boy of ten whose parents were unrelated. The condition is unknown in the family of either parent; the father had 14, the mother 6 sibs. The central blaze in the forehead hair arises from unpigmented skin, only the adjacent parts of the forehead being unpigmented. Pearson recorded another mutation.

A large family with white forelock and unpigmented spots on body and limbs is described from the Bergen district of Norway by Sundför (1939). In a strictly dominant pedigree there were 42 piebald descendants with 30 normal sibs in four generations. The original male had only normal ancestors and sibs, and must have been a mutation. The white hair is in a triangle with its base at the forehead and its apex toward the crown. Occasionally it extends to the vertex or is reduced to only a few white hairs. The skin of the central forehead is frequently unpigmented and sometimes this extends to the eyebrows. Spots on the body only "come out" after exposure to the sun, but the hair on these spots is white. Absence of white spots accompanying a white forelock can then only be proven when the body has been exposed to tanning. The original mutant was born in 1836, and the family tradition accounts for it by the folk-theory that his mother

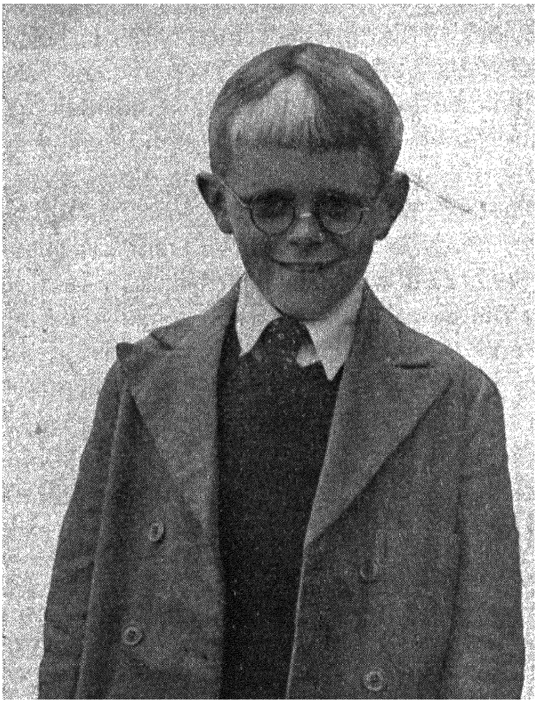

Fig. 103. White forelock mutation in a boy of ten. (After Nussey)

was frightened by a white horse before he was born. A family in Nebraska recorded by Fitch (1937) has 12 cases (8♂ 4♀) in five generations with strict dominance. The white forelock has been transmitted since the middle of the eighteenth century and is often accompanied by a few white spots on the body.

Thus it is clear that a white forelock with a white spotting pattern of the skin is fairly common — sufficiently so to account for a piebald pattern occasionally occurring in crosses with negroes.

That white forelock is also inherited as a simple dominant in a cross with the black race, is shown by the pedigree of a German slave-owner in Virginia, who had children by various Negro concubines (Cromwell, 1940). He had a white forelock and the hybrid descendants from his mating with one Negro woman show 13 with the forelock to 19 without it, in four generations. The descent is dominant, with one skip. In some cases the white patch extends over the forehead, but there is no evidence as to whether any of them had body patches. White forelock and the piebald skin pattern may be alleles.

As regards the racial distribution of albinism, there are several records, especially in American Indians, of tribes with a number of "white Indians." The Pearson monograph cites them. In connection with Dampier's expedition to Darien in 1681, there is a long and circumstantial account of the "white Indians," who could see better by moonlight, etc. There is a similar record for Brazil in 1775. Cortez, in connection with the Spanish conquest of Mexico, described Montezuma's palace as containing an entourage of albinos. In a similar way, in the Middle Ages, fools and dwarfs were considered a desirable accessory to the retinue of kings and nobles. As late as 1841, Catlin (1926) described a "white Indian tribe" in Upper Missouri containing many albinos. It appears that albinism is now most frequent among the Indians of Arizona and Mexico. Poole, in 1872, reported light-haired and fair Indians from Queen Charlotte Islands (Haida) and British Columbia.

The most striking case of albinism on record is that of the so-called white Indians of the San Blas coast and Darien. The earliest full account of them is by Wafer (1699), and the fullest recent description is by R. G. Harris (1926). Shrubsall, Haddon and Buxton (1924) published notes on their observations of several individuals and Harlan (1932) gives an illustrated account of them. They are a "race" of partial albinos, originating through mutation and perpetuated by inheritance, their peculiarities being recessive to the type. Their skin is white, with large freckle-like copper-colored spots. The hair may be yellow or may even show traces of brown. The iris is hazel, dark blue, or dark violet. They are strongly photophobic and so are at a great disadvantage by day in strong sunlight, and they are generally smaller than the type. In 1924 several were brought to the United States and Canada, where they were studied by anthropologists. Although marriages between albinos are prohibited by the tribe, and "white" women rarely marry brown men, yet they have persisted in numbers for at least three centuries. It is instructive to know that a recessive condition can persist and spread in a population in this way even although it is under serious natural disadvantages and is further prevented from increase by tribal law. This is possibly a case of "drift" (Sewall Wright).

There are said to be over 300 such white Indians. In a population of 20,100 Indians, Harris found 138 albinos, a frequency of 0.7 per cent. There is reason to suppose that the peculiar types among the Mandan Indians in North America may have originated and spread in similar fashion, although the possibility of early Nordic influx is not wholly excluded. We are thus furnished with an example of a racial color type of man in the making. Harris examined 309 offspring from matings of light brown and very light brown individuals, who were regarded as most likely to be heterozygous, and obtained 14.2 per cent of whites. The deficiency from 25 per cent may be due partly to their lesser viability under tropical conditions, but the pedigrees are consistent with a single genic difference and the light brown are probably not to be identified with heterozygotes.

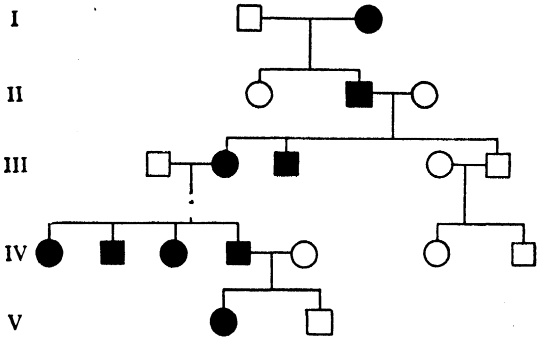

Fig. 104. Premature whitening of the hair. (After Hare)

Early graying (canities praematura) is a physiological inherited form of partial albinism. Hare (1929) described a family (Fig. 104) with 9 cases (4 ♂ 5 ♀) in five generations, inheritance dominant. In affected individuals the hair begins to turn gray at seventeen or eighteen and is white at twenty-five to twenty-six. Serebrovskaya (1929) has seven pedigrees with fifty cases. She finds two types, (1) spread evenly over the head, (2) localized at the temples. Both are controlled by a dominant autosomal gene. Woelfflin (1938) has four short pedigrees of dominant early graying. Whether in brown or blond hair, the change occurs equally early. Plummer (1937) cites a family in which one male in three successive generations turned white at about twenty-five years of age. The women were unaffected. It is claimed (Sieve, 1941) that the ingestion of *p*-amino benzoic acid will cause the repigmentation of hair. Black rats on a diet which is low in copper decrease their pigmentation to a silver gray (Gorter, 1935). Copper added to the diet restores the color. It probably acts as a catalyst in melanin production.

Albinism in Animals

That albinism is of very widespread occurrence in animals is well known. Such cases only will be referred to here as appear to have a bearing on the genetics of albinism in man. Other cases are referred to elsewhere (Gates, 1929). Albinos are described in a herd of Holstein cattle from Minnesota and Wisconsin (Cole, Van Lone and Johansson, 1934). At birth they were practically devoid of pigment, but they gradually developed some pigment in iris and hair, the coat becoming creamy. There is also a ghost pattern of white spotting which is inherited independently of albinism. They showed photophobia but their milk production was normal. The albinism in this herd was recessive and probably came from the same original mutation as that of another herd in southern Minnesota. Petersen *et al.* (1944), in a further study of albinism in Holsteins, Guernseys and Ayrshires, show that the ghost pattern gene probably produces its effect only in presence of the gene **B**, for black. In the ghost pattern area there is no difference in pigmentation but these hairs have a smaller medulla in females and none in males. In the Museum in Para, Brazil, I saw the skin of a black (melanic) jaguar in which a ghost pattern could be seen in an oblique light.

Piebald patterns are very widespread in domestic animals, such as horses, cattle, rabbits, dogs and cats and some breeds of sheep and pigs. The type of piebaldness varies from species to species, but it appears that in most domestic animals there is a dominant and a recessive type of piebald. In cattle, rabbits and sheep these are morphologically different.

Klemola (1933) describes three types of piebald pattern in horses:

1. A white blaze in the forehead with white muzzle and "socks." This is very common, is recessive to self-color and its heredity is complicated, with many genes and modifiers.
2. Piebald or skewbald, in which the white areas are mainly dorsal. This is dominant to self-color and is seen mainly in pampas and prairie horses and Shetland ponies.

3. Recessive piebald or splashed white, the colored areas mainly dorsal, the head generally white, with a "wall" eye. The dominant and recessive piebald patterns are more or less complementary in white distribution. The wall eye may be simply an unpigmented area extending to the iris, or it may be a separate gene dominant to splashed white. Probably self-color, dominant and recessive piebald and wall eye represent four allelic genes. In man, the piebald pattern appears to be always dominant. Some Shetland ponies are homozygous for the dominant spotting pattern.

In various animals albinism is linked with other features. In love birds (Kokenmüller, 1936) total albinism is sex-linked, so the recessive gene is located in the X-chromosome. Incomplete albinism is also a sex-linked recessive in the turkey (Hutt & Mueller, 1942). This gene leaves some pigment in the iris, but the birds are blind and 75 per cent of the females (which are heterozygous) die. A similar condition is found in fowls, but the retina is pigmented, the vision is not affected and the condition is not sublethal. Hutt and Mueller (1943) record three recent independent but identical albino mutations, all apparently in the same locus of the X-chromosome, in different breeds of fowls. Similarly the gene for white eyes is sex-linked in several species of Drosophila but is autosomal in two other genera of flies. We may suppose that in birds, unlike mammals, the gene for albinism is generally in the X-chromosome.

In the mouse, W. H. Gates (1931) has shown that the genes for albinism, shaker and pink eye are all in the same chromosome in that order, the cross-over value between shaker and albinism being 2.91 in the ♂ to 4.11 per cent in the ♀, while shaker and pink-eye show a cross-over value of 14.7. Shaker resembles Huntington's chorea in man and might be regarded as a parallel mutation, but shaker is recessive while Huntington's chorea is always dominant. The occurrence of albinism in any family with Huntington's chorea should make it possible to determine whether they are linked, as in the mouse. Pease (1928) showed that in rabbits the gene for albinism is linked with the genes for yellow fat and brown color, and Mohr found a recessive gene for yellow fat in the sheep of Iceland. As mapping of the chromosomes proceeds in mammal genetics, it will be possible to determine in how far parallel genetic conditions exist in man.

Keeler (1931) described a dominant spotting mutation in the house mouse. Animals homozygous for this gene were so anaemic that the condition was lethal. A recessive piebald spotting is also known, and Clark (1934) described a recessive bellyspot which was closely linked with recessive flexed-tail-anaemia. Both bellyspot and flextail have low penetrance, while the anaemia is inherited as a typical recessive. Murray and Green (1933) conclude that bellyspot is neither dominant nor recessive (perhaps an alternative expression for dominance with low penetrance). The symbols for these forms are **Ww** black-eyed white, **ss** piebald. Dunn described two modifiers of **ss** — white-face spotting and a white band around the body. Little described a frontal blaze with several modifying genes, also white tail tip and a white band on the tail. In bellyspot, the patches were larger and more frequent in males than females.

Barto and Huestis (1933) found a frontal star present in 3 per cent of the deer mice (Peromyscus) trapped in Oregon. They found that matings between starred as well as matings between non-starred mice could produce both starred and non-starred, so that multiple genes are probably involved. Individuals with large stars produce offspring with more and larger stars than animals with a small star. Albinism and pink-eyed pallid are linked in Peromyscus. Feldman (1936) found that piebaldism in a stock of *Peromyscus maniculatus rufinus* is due to two recessive genes which interact to produce a range of types, whereas in *P. m. bairdii* it is caused by a single dominant gene. Crosses between these stocks extended the range of variation to include completely white mice with black eyes, the two series giving additive effects.

Fortuyn (1939) describes a "mutation" in mice resembling *Mus musculus* but descended from a cross with the Chinese *M. wagneri*. From an agouti-and-white mother appeared a black-eyed-white son. He showed dominant white spotting, a condition known in China for centuries. It is probable that the dominant white spotting was inherited in some way from *M. wagneri*, but suppressed in the intervening generations. It is lethal in the homozygous condition.

Wright and Chase (1936) analyzed the spotted patterns in guinea pigs. SS is self-color but may show traces of white. Ss may show any grade from self-color to 95 per cent white. ss also, while often white, may range from well marked white to near self-color. There is a multiplicity of minor genes with additive effects and little or no dominance. ss can be shifted from 10 to 97 per cent white by combinations of these genes, and SS may show a little white in the presence of an extreme array of modifiers. There is also a great amount of non-genetic variation, about 58 per cent of the variance in a typical stock being of this kind. Unlike mice, female guinea pigs show slightly more white than males.

Blunn and Howell (1936) studied the white facial markings in 477 Arabian horses. They found that star, strip, snip and chin spot are different patterns conditioned by modifiers of a general factor for white markings. The first three were dominant, the last apparently recessive.

Hutt (1945) records an albino mud-puppy (*Necturus maculosus*). Albinotic salamanders (*Eurycea bislineata*) and frogs (*Rana temporaria*) are known. In *Alytes obstetricans* and the axolotl (*Ambystoma tigrinum*) albinism is known to be recessive.

The breeding of foxes has led to the detection of certain new color mutations. The silver fox is a color variety of the red fox, *Vulpes vulpes*, which extends all over Europe, northern Asia and North America. The silver fox in captivity has produced three mutations to platinum — in Norway, Canada and the United States respectively. Platinum is a dilution of silver, but the homozygote is pure white and lethal. Cole and Shackelford (1943) show that white-face is another mutant from silver which is also white and lethal in the homozygous condition. Platinum and white-face are assumed to be alleles, and the authors suggest that they may represent a progressive chromosome deficiency. Another white-faced strain is found to be in another chromosome. Each of these types occasionally has blue eyes, especially when there is more white on the face, and sometimes there is heterochromia iridis. White-ear foxes are found to be more nervous in temperament.

LITERATURE

Atgier, M. 1910. Un negre blanc. *Bull. et Mem. Soc. Anthrop. Paris* 1:451–455. Fig. 1.

Barto, E. & Huestis, R. R. 1933. Inheritance of a white star in the deer mouse. *J. Hered.* 24:245–248. Fig. 1.

Biegel, H. 1868. Albinismus und Nigrismus. *Arch. f. Path. Anat.* 43:529–533. Pls. 16.

Blunn, C. T. & Howell, C. E. 1936. The inheritance of white facial markings in Arabian horses. *J. Hered.* 27:293–299. Fig. 1.

Bond, C. J. 1912. On heterochromidia iridis in man and animals from the genetic point of view. *J. Genet.* 2:99–129. Pls. 4.

Boyle, F. 1865. *Adventures amongst the Dyaks of Borneo.* London. Pp. 324.

*Burton, R. 1863. *Wanderings in West Africa.* London. Vol. II.

Catlin, G. 1926. *North American Indians.* Edinburgh: John Grant, 2 vols.

Christianson, E. 1941. Albinism: observations in two native Seychelles families. *Brit. Med. J.* i. 556.

Clark, F. H. 1934. The inheritance and linkage relations of a new recessive spotting in the house mouse. *Genetics* 19:365–393. Fig. 3.

Cockayne, E. A. 1914. A piebald family. *Biometrika* 10:197–200. Pls. 9.

———. 1933. *Inherited Abnormalities of the Skin and Its Appendages.* Oxford Press. Pp. 394.

———. 1935. A second piebald family from Suffolk. *Biometrika* 27:1–4. Pls. 2.

Cole, L. J. & Shackelford, R. M. 1943. White spotting in the fox. *Amer. Nat.* 77:289–321. Figs. 11.

Cole, L. J., Van Lone, E. E. & Johansson, I. 1934. Albinotic dilution of color in cattle. *J. Hered.* 25:145–156. Figs. 6.

Cromwell, A. M. 1940. Inheritance of a white forelock in a mulatto family. *J. Hered.* 31:94–96. Fig. 1.

Davenport, C. B. 1916. Heredity of albinism. *J. Hered.* 7:221–223. Figs. 3.

Davenport, G. C. & Davenport, C. B. 1910. Inheritance of albinism. *Amer. Nat.* 44:705–731.

Ebstein, E. & Günther, H. 1914. Klinische Beobachtungen über Albinismus. *Zeits. f. Morph. u. Anthrop.* 17:357–380. Pls. 2, figs. 2.

Feldman, H. W. 1936. Piebald characters of the deer mouse. *J. Hered.* 27:300–304. Fig. 1.

Fitch, L. 1937. Inheritance of a white forelock. *J. Hered.* 28:413–414. Figs. 2.

Fortuyn, A. B. D. 1939. A mutation from agouti with recessive spotting to dominant spotting in *Mus musculus. Genetica* 21:92–96. Figs. 2.

Gamble, W. E. 1924. Albinism of the eyes without involvement of the hair or skin. *Ophthal. Rec.* 23:237–239.

Gates, R. R. 1936. Recent progress in blood group investigations. *Genetica* 18:47–65.

Gates, W. H. 1931. Linkage of the factor shaker with albinism and pink-eye in the house mouse. *Zeits. f. Abst. u. Vererb.* 59:220–226.

Gorter, F. J. 1935. Depigmentation, a new dietary deficiency disease cured by copper. *Nature* 136:185.

Haldane, J. B. S. 1938. The estimation of the frequencies of recessive conditions in man. *Ann. of Eugen.* 8:255–262.

Hare, H. J. H. 1929. Premature whitening of the hair. *J. Hered.* 20:31–32. Fig. 1.

Harlan, H. V. 1932. Early references to the white Indians of Panama. *J. Hered.* 23:319–322. Figs. 3.

Harman, N. 1909. Six generations of piebalds. *Trans. Ophthal. Soc. U. K.* 29:25–33.

Harris, R. G. 1926. The San Blas Indians. *Am. J. Phys. Anthrop.* 9:17–63. Figs. 5.

Hogben, L. T. 1931. The genetic analysis of familial traits. I. Single-gene substitutions. *J. Genet.* 25:97–112.

Holmes, S. J. & Schofield, R. O. 1917. Inheritance of white forelock. *J. Hered.* 8:359–360. Fig. 1.

Hutt, F. B. 1945. Complete albinism in the mud-puppy, Necturus. *J. Hered.* 36:145–147. Fig. 1.

Hutt, F. B. & Mueller, C. D. 1942. Sex-linked albinism in the turkey. *J. Hered.* 33:69–77. Figs. 4.

———. 1943. Independent identical mutations to albinism in the sex chromosome of the fowl. *Amer. Nat.* 77:181–184.

Keeler, C. E. 1931. A new mutation to "dominant spotting" in the house mouse. *J. Hered.* 22:273–276. Figs. 2.

———. 1934. The heredity of a congenital white spotting in negroes. *J. Am. Med. Assn.* 103:179–180. Figs. 2.

Klemola, V. 1933. The "pied" and "splashed white" patterns in horses and ponies. *J. Hered.* 24:65–69. Figs. 4.

Kokenmüller, K. 1936. Geschlechtsgebundene Vererbung bei der total-albinotischen Aberration des *Melopsittacus undulatus* (Shaw). *Zeits. Abst. u. Vererb.* 71:299–302.

Lange, W. 1935. Beitrag zum Albinismus. *Arch. f. Rass. u. Ges.-Biol.* 25:381–382.

Meirowsky, E. & Spickernagel. 1926. Über Vererbung und Lokalisation der Scheckenbildung sowie ihre Bedeutung fur die Naevus-ätiologie. *Arch. f. Derm. u. Syph.* 150:384–392. Figs. 9.

Miller, N. 1915. Heredity of white forelock. *J. Hered.* 6:165–169. Figs. 4.

Morgan, J. 1786. Some account of a motley colored or pye negro girl and a mulatto boy, exhibited before the Society in the month of May, 1784. *Trans. Amer. Phil. Soc.* 2:392–395.

Murray, J. M. & Green, C. V. 1933. Inheritance of ventral spotting in mice. *Genetics* 18:481–486.

Nussey, A. M. 1938a. A piebald family. *Biometrika* 30:65–67. Pl. 1.

———. 1938b. White forelock, a new mutation. *Lancet* 235:947–948. Fig. 1.

Pardo-Costello, V. 1926. Congenital partial albinism. *Arch. Derm. & Syph.* 14:173–177. Figs. 3.

Parsons, James. 1766. An account of the white negro shewn before the Royal Society. *Phil. Trans. Roy. Soc.* 55:45–53.

Pearson, K. 1913. Note on the Honduras piebald. *Biometrika* 9:330–331. Pls. 4.

———. 1921. A new white-lock family (Barton's case). *Biometrika* 13:347–349. Pls. 2.

Pearson, Nettleship & Usher. 1911–1913. A monograph on albinism. *Drapers Company Research Memoirs.* Cambridge Press.

Pearson, K. & Usher, C. H. 1929. Albinism in dogs. *Biometrika* 21:144–163. Pls. 8.

Pease, M. S. 1928. Yellow fat in rabbits, a linked character? *Zeits. f. Abst. u. Vererb.* Supptl. vol. 2:1153–1156.

Petersen, W. E., Gilmore, L. O., Fitch, J. B. & Winters, L. M. 1944. Albinism in cattle. *J. Hered.* 35:135–144. Figs. 8.

Pipkin, A. C. & Pipkin, S. B. 1942. Albinism in negroes. *J. Hered.* 33:419–427. Figs. 7.

———. 1943. Ear pits and albinism in a negro family. *J. Hered.* 34:240–242. Figs. 6.

———. 1944. Hair of albino negroes. *J. Hered.* 35:201–206. Figs. 5.

Plummer, S. 1937. Family with premature white hair. *Eugen. News* 22:108–109.

Rizzoli, F. 1877. Ciocca di capelli bianchi alle fronte congenita ed ereditaria. *Boll. Sci. Med. Bologna* Sec. V. 23:102–103.

Sanders, J. 1934. A family with albinismus conscriptus. *Genetica* 16:435–439. Figs. 10.

———. 1935. Two families with albinismus conscriptus. *Genetica* 17:185–190. Figs. 10.

———. 1938. Die Heredität des Albinismus. *Genetica* 20:97–120. Figs. 39.

Sedgwick, W. 1861. On sexual limitation in hereditary disease. *Brit. & Foreign Med.-Chir. Rev.* 27:477–498, 28:198–214.

Seligman, C. G. 1902. A note on albinism, with especial reference to its racial characteristics among Melanesians and Polynesians. *Lancet* ii. 803–805. Figs. 4.

Serebrovskaya, R. I. 1929. Die Vererbung von Canities praecox. *Med. Biol. J.* (Russian). Pp. 83–89.

Shrubsall, F. C., Haddon, A. C. & Buxton, L. H. D. 1924. The "White Indians" of Panama. *Man* 24:162–164. Figs. 4.

Sieve, B. F. 1941. Clinical achromatrichia. *Science* 94:257–258.

Simpson, Q. I. & Castle, W. E. 1913. A family of spotted negroes. *Amer. Nat.* 67:50–56. Figs. 4.

Stannus, H. S. 1913. Anomalies of pigmentation among natives of Nyasaland. *Biometrika* 9:333–365. Pls. 10.

Stiven, H. E. S. 1923. A Sudanese albino. *Lancet.* 204:648. Fig. 1.

Sundför, H. 1939. A pedigree of skin-spotting in man. *J. Hered.* 30:67–77. Figs. 24.

Swab, C. M. 1931. Albinism of the progeny of negroes and white parents. *Trans. Amer. Ophth. Soc.* 29:365–371. Figs. 2.

Waardenburg, P. J. 1932. Das menschliche Auge und seine Erbanlagen. *Bibliogr. Genet.* 7:1–631. Figs. 197.

———. 1935. Vererbungsergebnisse und -Probleme am menschlichen Auge. *Zeits. f. Abst. u. Vererb.* 70:358–376.

Wafer, Lionel. 1903. (Rep. from original edition of 1699.) *A new voyage and description of the Isthmus of America.* Cleveland.

Windle, E. 1935. Three generations of albinism and twinning. *J. Hered.* 26:23–24. Fig. 1.

Wlissidis, Thr. 1928. Ueber einen Fall von allgemeinem Albinismus mit Nystagmus. *Verh. V. Internat. Kongr. Vererb.* 2:1601–1602. Fig. 1.

Woelfflin, E. 1938. Über Vererbung von frühzeitigen Ergrauen bzw. Weisswerden der Kopfhaare. *Arch. f. Rass. u. Ges.-Biol.* 32:170–173.

Wright, S. & Chase, H. B. 1936. On the genetics of the spotted pattern of the guinea pig. *Genetics* 21:758–787.

Zimmermann, H. 1923. Über menschlichen Albinismus. *Arch. f. Rass. u. Ges.-Biol.* 15:113–136. Figs. 6.

Chapter X

ABNORMALITIES AND DISEASES OF THE SKIN, HAIR, NAILS AND TEETH

ABNORMAL conditions of the skin are very numerous and some of them very rare. As the inheritance of skin diseases has been fully treated by Cockayne (1933), the results in this field will be summarized here, and fuller references can be obtained from that work. The more important subsequent papers will be referred to here. Garnier (1945) shows that such dermatoses as eczema, psoriasis, acne and even herpes simplex are partly controlled, at least in women, by the gonadal hormones.

Freckles are of frequent occurrence in the white races. They are patches of pigment in the basal layer of the epidermis on exposed parts, particularly the hands, face and neck. They appear in children and gradually decrease after adulthood is reached. They are well known to be commoner in red-haired persons, but there appears to be no correlation between freckles and eye color. Freckling is inherited as a simple dominant, perhaps showing genetical linkage with red hair or more likely a pleiotropic effect. Freckling in children is also associated with less power of immunization against tuberculosis.

Scheidt (1925) published two pedigrees of freckling. In one family there were 12 cases (4♂ 8♀) in four generations, the inheritance dominant. The freckled members all had red-brown hair except one whose hair was red-blond, while the non-freckled members were all blond. The second family had only five cases of freckling in three generations. The pedigree of Meirowsky had 62 cases in five generations, 8 of them having red hair while none of the unfreckled had red hair. Decking (1926) found freckles a useful character in diagnosing twins as monozygotic (MZ) or dizygotic (DZ). He examined school children, finding in 62 pairs of monozygotic twins that the freckles corresponded rather closely in position and degree of conspicuousness. In 22 pairs there were no freckles, 9 pairs had only traces around the nose, 9 had a few scattered on the face, in 18 pairs the freckles were moderately developed and 4 pairs were strongly freckled. Among 30 pairs of DZ twins, both were unfreckled in 6 pairs, and in 7 pairs one was freckled and the other unfreckled. Only 5 pairs agreed in degree of freckling, the others showing more marked differences than occurred in the identical twins.

In Japan and the South Sea Islands freckling appears to be recessive. Ten Japanese families have been described with freckles on the nose, forehead, cheeks, lips, ears, buttocks, thighs, the extensor surfaces of the arms and the dorsum of the hands and feet.

Leucoderma or *vitiligo* is a disease producing depigmentation of portions of the skin, especially in tropical peoples. Its occurrence in families, however, indicates that a dominantly inherited condition of the skin is present which renders it more susceptible to depigmentation. The attacks of certain fungi also cause loss of skin color in tropical peoples. Görl (1934) described a family with five cases in three generations having smooth light patches on the skin.

Under the term *dyschromatosis universalis*, Toyama *et al.* (1934) describe an inherited condition in two Japanese families, in which sharply delimited pigment flecks from the size of a rice grain to that of a bean are scattered over the entire body except the palms and soles. It occurred (1) in a mother and two male children, (2) in a mother and two daughters with four normal sibs.

Lettsom (1772) recorded the case of a girl,[1] eight years old, in Bedfordshire, with swarthy skin on one side of the body and long, dark hair on the corresponding side of the head. On the other side the skin was fair and the hair lighter, short and frizzled. This was probably a somatic mutation or segregation. Leber (1936) reports a family with universal hereditary *melanosis*, an irregular dominant with twenty-two cases in six generations. In two members of the last generation depigmentation appeared later.

A modern case of a bilateral human mosaic has recently been described (Zlotnikoff, 1945) from the Tambov district of Russia. In a young woman 24 years old, whose numerous relatives were all normal, the right side of the body was normal, the eye on that side gray. On the left side (sharply down the sagittal line) the skin was striped with naevus-like patches which itched, the left leg being all brown, the body patches dense brown, café-au-lait, or crimson. The sweat on this side was more copious and brown in color, the left eye dark brown. The head hair was partly bald (also abundant?) and chestnut in color on the left side, scarce and light red on the right side. The most probable explanation appears to be a pleiotropic mutation in one blastomere at the 2-cell stage.

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[1] Another girl of thirteen was described having very dark complexion and jet black hair. She arose one morning (having had no fright) with a white lock of hair about 1½ in. wide on the side of her head. A similar change soon developed on the other side. These changes continued until the hair appeared in stripes of white and black, and in about seven years it was all white. Her complexion also changed to fair, but the eyebrows stayed black, the lashes white, her eye color remaining black and her health good.

Lipoidosis of the skin and mucous membranes should probably be classed as a metabolic error, but the lipoids accumulate in the skin, forming yellow papules on the face and scalp, warty excrescences on the fingers and small bluish-violet tumors on the elbows. The mucous membrane of the mouth and larynx also becomes thickly studded with small, yellowish-white plaques. The lesions are present at birth, together with laryngeal tumors. A phosphatide lipoid is present and the condition resembles xanthoma tuberosum multiplex.

In the Swiss family of Miescher (1925) the parents were first cousins and two sons and two daughters were affected in a sibship of twelve. The condition was like congenital *ichthyosiform erythrodermia*: universal keratosis of the skin, with increased pigmentation, papillary projections on the knees and elbows, thickening of the nasolabial folds, with yellow coloration and thickening of the palms and soles. There was hyperidrosis (excessive sweating) of the palms and soles. In another Swiss family (Nager, 1925) the conditions were somewhat different. In a sibship of seventeen children, two pairs of twins died of asphyxia at birth, four others were affected, three of them with *stenosis of the larynx*, necessitating tracheotomy. They also had hyperkeratosis of the palms and soles and spontaneous bulla formation. The parents were again first cousins, the condition being a simple recessive. Roessle named it *dystrophia pachydermica cutis et mucosae progressiva.*

Xeroderma pigmentosum (Kaposi's dermatosis) consists essentially in brown spots and ulcers of the skin and may also be fundamentally an error of metabolism. Cases are normal when born, but develop photophobia in a few weeks. Then erythema (reddening) appears in the exposed parts of the skin and the conjunctiva becomes red. Then large freckles develop and with more exposure white pits and telangiectases appear on the skin. Generally the condition develops into an epithelioma or sarcoma later. Two-thirds of those afflicted die before the age of fifteen, but they may live to twenty or even forty years of age although they rarely marry. The sibs of affected individuals frequently have heavy freckling and naevi. This probably represents the heterozygous condition, since the gene is recessive. It resembles porphyria (*q.v.*) in that sunlight is necessary to bring out the lesions. Erythema, pigmentation, atrophy and tumor formation may all occur simultaneously in different portions of the skin. The freckling is more marked than the ordinary type and is not associated with red hair or with skin color.

Taylor (1888) found forty recorded cases and described seven cases of children with xeroderma pigmentosum. In one family three out of five children were affected, with dark spots on their faces. Another family had two affected children. In the third family, a boy, his sister and five cousins were affected, and only one of them had light hair. This suggests possible linkage with hair color.

Siemens and Kohn (1925) collected 333 cases in 222 families. Of these, 187 were familial (in 76 families), the rest solitary. In the latest enumeration there were 193♂ : 182♀ affected. A pedigree of Siemens is given in Fig. 105. The long series of sibships of Siemens and Kohn was found by Cockayne to give a ratio, affected : normal, of 1 : 1.7 and in 17 later families 1 : 1.9, instead of 1 : 3 as might be expected for a recessive. The difference is explained on a statistical basis and is due to the fact that some marriages between two individuals who are normal but both heterozygous nevertheless produce only normal children (especially in small families), and are therefore not recognized as families whose children should be added to the normals. In all such cases of a recessive gene it is found that when only the larger sibships are considered the ratio approaches close to 1 : 3. Thus, taking sibships of 6 or more children in the present case gives a ratio of 107 : 288 or 1 : 2.69, and sibships of 8 or more (71 : 209) give a ratio of 1 : 2.9.

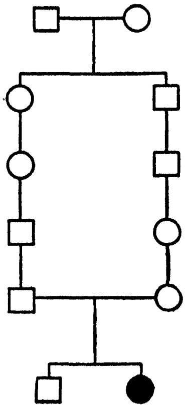

Fig. 105. Recessive xeroderma pigmentosum. (After Siemens)

Another feature connected with a recessive gene is that the frequency of consanguinity of the parents is higher than in the general population, but unfortunately in the past there has been frequent failure to recognize the need for recording the presence or absence of consanguinity in such cases. The few children of persons with xeroderma pigmentosum are always free from it, as would be expected of a rare recessive. It is not much associated with other defects, but adherent ear lobes and mental deficiency have been recorded. More recent evidence indicates that while this disease is recessive it is also partially sex-linked and therefore not autosomal (see p. 76). Macklin (1944) finds that in eighteen families the inheritance is compatible with incomplete sex-linkage, i.e., when the father is related to his wife through his mother more daughters than sons are affected, when through the father more sons than daughters are affected. (See also Chap. IV, p. 78.)

Xeroderma pigmentosum is found in many European races, but appears to be commonest in Jews. It is also found in the Arabs of Tunisia, in Japanese and (one case) in Chinese. It is probably an incomplete recessive, as already mentioned, but in certain cases penetrance may fail even in the homozygous condition. Mohr (1926) points out that as the death-rate of affected children is very high, the condition is essentially sublethal. Macklin (1936) finds that in 21.2 per cent of cases the parents are consanguineous, and that both sexes are equally affected.

Endothelioma simplex is a rare condition in which small skin tumors appear as papules from the size of a pinhead to a lentil, soft and elastic, the color rose-red, brown, yellow or skin color. Wise (1919) described a family in which the father and three sons were affected, two daughters normal.

Multiple cavernous *angiomata* (tumors made up of blood vessels) of the sweat glands were described by Archer (1927) in two brothers who had normal parents and nine normal sibs. The angiomata were found on the lower thorax, abdomen and buttocks, the mucous membrane of the lips, cheeks and soft palate being involved. They formed great numbers of purplish spots at the opening of the sweat glands. These structures differ from telangiectases. One brother had hemiplegia and dementia, probably from angiomata of the meninges. The condition is presumably recessive.

Epidermolysis bullosa (pemphigus hereditarius) was described by Goldschneider in 1882. Cockayne gives an extensive account of this rare hereditary disease. There are two forms, simple and dystrophic, the latter occurring in both dominant and recessive forms and with certain inherited variations as well. The formation of bullae or blisters filled with watery fluid is the most striking feature in all.

In the simplex form the bullae arise on the skin only and heal without leaving scars. They can be produced by injury or friction. In the dystrophic form they arise also on the mucous membrane and generally leave scars. These bullae are also deeper, between the epidermis and corium or (in Wende's case) in the corium, and they can scarcely be produced by injury.

The exact cause of bulla formation remains uncertain. The excess fluid present in the skin probably exudes easily from the blood vessels, and the exudation may be made easier by a deficiency of elastic tissue. But there are certain resemblances between epidermolysis bullosa and porphyrinuria, and possibly the basic defect is in metabolism and not in skin structure or in the vasomotor control of the blood vessels. This view is supported by the occurrence of bullae in crops, often preceded by a feeling of malaise. Thoroczkay (1940) describes associated bone changes.

The dominant and recessive forms of epidermolysis bullosa dystrophica show certain clinical differences. The sex-linked form described by Mendes da Costa and van der Valk in 1908 in a Dutch family also differs clinically and is known as *typus maculatus*. There were seven cases (all males) in one generation (four sibships). The affected children showed lesions at three months, with pigmentation and acrocyanosis. Bullae could be produced on the cyanotic parts by rubbing the skin. The hands were short with tapering finger-tips, short nails, hypotrichosis, palms and soles turgid and shiny.

The *simplex* form is frequently accompanied by hyperidrosis (excessive sweating). Cockayne reports a total of 268 hereditary cases. It is generally dominant, with an excess of affected males (150 : 100) and an occasional skip. Bonajuti reported a large family in 1890 (pedigree in Gossage, 1908) with 31 cases (16♂ 15♀) in five generations, dominant with two skips. Castle (1925) reported a strictly dominant pedigree with 11 cases (6♂ 5♀) in four generations, and Bamber (1935) a family with 12 cases (7♂ 5♀) in four generations and no skip, the sibships totalling 11 affected : 12 normal. Blisters arise from trivial injuries and may begin shortly after birth, from the child sucking its fingers. In this family the condition disappeared when adult age was reached.

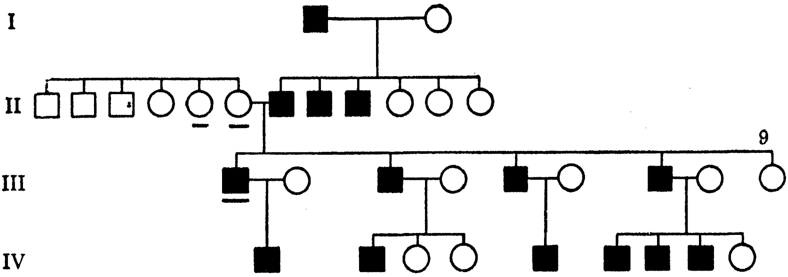

Fig. 106. Holandric inheritance of epidermolysis bullosa simplex. (After Yaffe)

Yaffe (1942) reports a family of soldiers in India and Jamaica in which all the males suffer from epidermolysis bullosa simplex from infancy (Fig. 106). Their knees blister when they begin to creep and their feet blister excessively when they march, but they are not otherwise inconvenienced. This adds one more to the list of genes which are found in the Y-chromosome and show holandric transmission. The pedigree includes three cases (two sisters and the son of one, II. 5, 6 and III. 1 in the pedigree) who died from cancer of the throat. As in all other holandric pedigrees, while the females are all normal their descendants are not recorded, and the possibility that half their sons inherited the disease is not excluded.[2] Greenberg (1944) reports 5 cases (whites) of foot blisters from marching, among 2281 dermatological cases at a camp in South Carolina. These mild (dominant) cases are probably more frequent than generally recognized. The 5 cases had at least 24 affected relatives (dominant in each family). The condition is worse in hot weather.

In *epidermolysis bullosa dystrophica* the recessive form is more severe

[2] Correspondence elicits the further information that the normal sister (III. 9) had three normal daughters and an affected son. Hence the gene has crossed over from the Y- to the X-chromosome.

than the dominant, the nails being always absent or deformed, the skin more often cyanotic and pigmentation excessive or lacking, the teeth often abnormal and defective. Many die before puberty, but some marry and reproduce, and there are many consanguineous marriages. There is evidence that some recessive forms of epidermolysis bullosa are partially sex-linked, i.e., the gene is in the X-chromosome (see p. 76). Jenny (1927) described a very severe form which is fatal in a few weeks or months after birth, so the gene may be regarded as lethal. The pedigree of this family was traced back into the sixteenth century (Fig. 3, p. 9) through twelve generations. Several cousin marriages and intermarriage with another family finally brought the recessive gene to the surface. Jenny produced another almost equally extensive pedigree with four cases arising from intermarriage among the descendants of one couple eight generations back. A closely related recessive form was described in a brother and sister with a normal brother and parents, by Heinrichsbauer (1928).

Another form of epidermolysis bullosa dystrophica was described by Guy (1927) in three boys. The bullae were subcorneal, associated with congenital alopecia and enlarged thymus. A distinct form was also described by Wende (1902) in two brothers of an Irish-American family. These are all recessive and may be allelic mutations. Smith (1934) cited a boy with epidermolysis bullosa and psoriasis whose normal parents were first cousins. His maternal aunt had psoriasis. Another case, presumably also recessive, was cited in a child of first cousins. Steggerda (1930) described five cases (dominant) of a mild form in which a slight bruise produced a "water blister" which turned "black and blue" and left a scar.

The severe dystrophic form of epidermolysis bullosa is generally recessive, but Hoffman (1926), who records an extensive pedigree with four cases of the recessive form arising in four intermarried families, also describes a dominant family with three cases in three generations. The symptoms were relatively mild, however, although the finger-nails were affected and there were facial scars as well as occasional bullae in the mouth. Haldane (1936) finds the recessive dystrophic form to be partially sex-linked. (See Chap. IV.)

Cockayne (1938) described two families in London with an atypical condition in which only the feet, and to a less extent the hands, suffered from severe blistering (see also p. 76). Haldane and Poole (1942) describe a family from Wiltshire with the same peculiarity, for which they propose the name *Cockayne's disease.* In all three families the condition is strictly dominant and in Haldane's family it arose as a mutation. There were 18 cases (10♂ 8♀) in four generations. The gene may be allelic to some of the other forms of epidermolysis bullosa.

The localizing effect is evidently a part of the gene and not due to modifiers. A similar family with blisters on hands and feet is described from West Virginia (Cartledge and Myers, 1943). The original ancestor, born in 1762, married twice and both lines of descent show the blisters. There are 40 cases (20♂ 20♀) in six generations, the sibships numbering 39 affected : 38 normal, strictly dominant, but the homozygous condition is unknown. Frank (1943) records a mild form occurring as a dominant in two families having respectively 19 cases (14♂ 5♀) in four generations and 16 cases (11♂ 5♀) in three generations. Confined mainly to the feet, it occurred only in warm weather. Franks and Davis (1943) compiled another pedigree with 13 cases (9♂ 4♀) in five generations.

The recessive type has been found in Anglo-Saxons, Scandinavians, French, Italians, Jews and Japanese.

Nager (1925) described a Swiss family with recessive *epidermolysis of the larynx*. The parents, who were cousins, had seventeen children. Three acquired the condition in middle life. One of them as a child could not move its tongue freely; another had hyperkeratotic palms and soles, with nails, knees and elbows also affected, and the third lost his voice at forty. Another sib had the same affliction and two pairs of twins died from asphyxiation a few days after birth. Thus there were 8 affected : 9 normal.

Hydroa aestivale may be related to epidermolysis bullosa. Bullous eruptions containing a yellowish fluid develop on the hands and feet but produce no scars. In a family described by Griffith (1936) the attacks recur every summer. The inheritance was dominant, with six cases (5♂ 1♀) in three generations.

Hereditary oedema (Milroy's disease) was originally described by Milroy (1892). The original account of the disease included a pedigree with twenty-two cases in six generations of a family numbering ninety-seven persons. The oedema (dropsy) or swelling may be present at birth or may arise in childhood or early adulthood. One or both legs swell to enormous size (elephantiasis) through the effusion of watery liquid into the connective tissue. The swelling is not painful or tender. Affected persons bandage their legs and live to old age, but the swelling never rises above Poupart's ligament. Nonne (1891) had already described a German family with 9 cases (3♂ 6♀) in four generations. Meige (1898) recorded a French family with 8 cases (4♂ 4♀) in four generations, developing at puberty, and on the Continent the disease is frequently named after him. The onset was at puberty, only legs and feet affected, some cases only up to the knee, one unilateral. Meige regarded it as trophoedema of neuropathic origin. Rolleston (1902) found the non-congenital form in mother, son and daughter. Hope and French (1908) traced a family with thirteen cases in five generations in which it appeared in infancy to early manhood and developed painful, acute attacks not found in other families. Bulloch (1909) collected nine pedigrees of this trophoedema and found it rather more common in females than in males. Milroy (1928), in a further account of his original family, located thirty more descendants in the fifth, sixth and seventh generations, but only two more cases (children of his original patient), so the condition seems to be disappearing in this family. McGuire and Zeek (1932) described a family with eight cases in three generations. A boy of fifteen years in this family (Fig. 107) had elephantiasis of the legs with Fröhlich's fat boy syndrome. Masses of tissue were removed by the Kondoleon operation and the pathologic changes in the skin are described. Faber and Lusignan's (1933) family came from the French Pyrenees (three

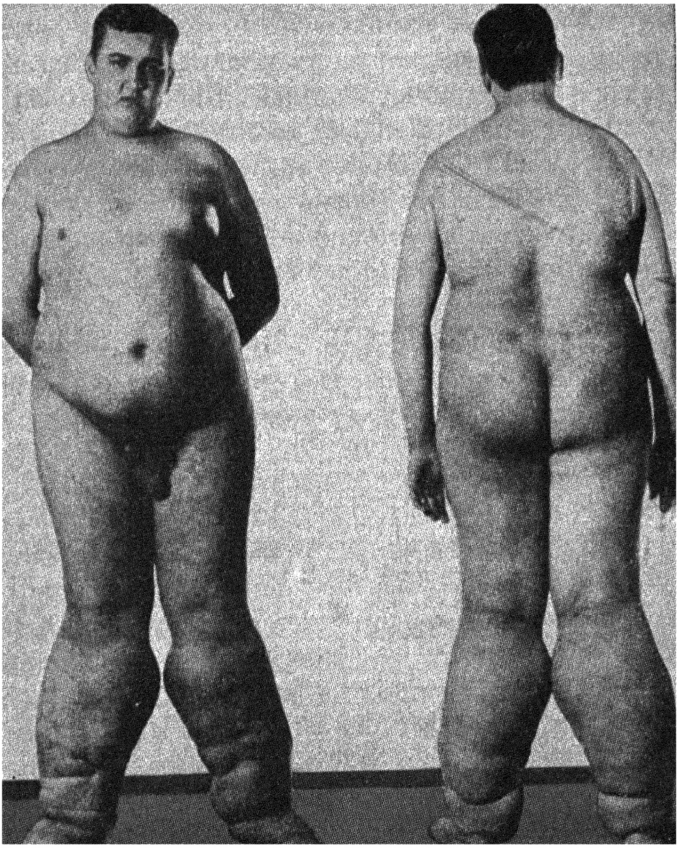

Fig. 107. Boy of 15 with elephantiasis of the legs (Milroy's disease). (After McGuire and Zeek)

cases in three generations). These authors found 133 cases recorded in 20 families, the sexes equally affected. Drewes (1939) described elephantiasis of the legs only in a brother and sister, beginning at fourteen to fifteen years. The mother had a light form of it. There have been many theories of the etiology of this disease — nervous, lymphatic, vascular, endocrine, sympathetic, but no explanation.

The inheritance is clearly dominant, with a few skips. Cockayne (1933) separates the congenital condition from the trophoedema with late onset. He tabulated (from Bulloch, 1909) six congenital families with 29 affected : 44 normal in sibships, 12 ♂ : 17 ♀. Late onset, in seven families, gives 36 affected : 45 normal, 11 ♂ : 25 ♀. The large excess of affected females might mean a second gene in the X-chromosome or it may simply mean that the female sex is more susceptible.

Many different forms and degrees of *keratosis* (tylosis) or abnormal thickening of the skin exist. *Keratosis follicularis* (Darier's disease) is also known by various other names such as *ichthyosis follicularis.* It is one of the extreme forms and is characterized by papules containing scabby crusts and is due to cornification of the epithelial layers of the skin. It is accompanied by cell degeneration in the upper part of the hair follicles and sweat ducts, and may affect the face, scalp, back, abdomen and other parts. The lesions begin in childhood with papule formation at the opening of the sebaceous and sweat glands. The mucous membrane may also be affected. In severe cases the stature is small and mental deficiency is present. The disease is inherited as a dominant in Anglo-Saxons, Latins, Slavs, Jews and Japanese. Cockayne tabulated 16 families with 45 cases (23 ♂ 21 ♀) fully reported, and 34 other families with 102 cases (46 ♂ : 46 ♀ : 10 unstated). One case apparently arose as a mutation from normal parents. Although it appears to be a strict dominant with no skips, it usually persists for only two (occasionally three) generations, apparently because of lack of reproduction by affected individuals. It is not an irregular dominant, as Fischer (1925) thinks, and the sexes are equally affected. Fischer collected 120 cases, 32 of them familial and 88 solitary. If the latter are really all mutations, it would indicate a high mutation-rate for this disease. There is much need for fuller study of the antecedents in every case of an apparent dominant mutation (many of which now exist in the literature) with the possibility of throwing light on the origin. Keratosis follicularis has also been recorded as a sex-linked recessive. Laméris (1905) has a pedigree with twelve cases, all males, in four generations in Utrecht. There was hypotrichosis of the scalp, degeneration of the cornea and hypoplasia of the lower jaw. In a study of ten cases, Peck, Glick, Sobotka and Chargin (1943) find that keratosis follicularis is a disease of vitamin A deficiency, with an inherited or acquired weakness in absorption of vitamin A or in conversion of the provitamin to the vitamin. It was recently found that half the native troops in Syria from East Africa had symptoms of keratosis follicularis, probably from lack of vitamin A.

MacLeod (1909) described three brothers with non-inflammatory *keratosis pilaris.* The parents and two other brothers were normal. The three brothers showed absence of eyelashes and eyebrows and more or less completely bald scalp. In most parts of the body the hairs were replaced by pinhead papules with a horny plug which could be removed. The skin was dry, hairy, more or less scaly, reaching a condition of mild ichthyosis on the knees and thighs. The condition was probably recessive. Siemens (1925) described a family in Utrecht with twelve cases (all males) of *keratosis follicularis spinulosa decalvans* in three generations. The inheritance was recessive sex-linked, the keratosis being accompanied by degeneration of the cornea and progressive loss of hair (alopecia). *Keratosis supra-follicularis* (Unna) goes under several other names. Horny plugs at the opening of the hair follicles form acuminate papules. There are several related conditions with different grades of severity, all uniform in each family. Szodoray (1939) describes the second case in Hungary under the name *trichostasis spinulosa.* There were four to eight hairs in a follicle. He states that in European cases the condition is mostly localized on the trunk, while in American cases it is generally on the face. *Ichthyosis follicularis with alopecia* has been recorded in three families having respectively three brothers, two brothers and three siblings from normal parents. The children are born bald or the hair falls out in childhood, the eyebrows and eyelashes also being lost. The nails are normal and the condition is presumably recessive.

Keratosis pilaris or *ulerythema ophryogenes* (Taenzer) differs from ichthyosis follicularis in that scarring occurs around the mouths of the hair follicles. Galewsky's two pedigrees show dominant inheritance while ichthyosis follicularis is recessive. In one pedigree there were 8 cases (4 ♂ 4 ♀) in three generations.

Keratosis follicularis spinulosa cum ophiasi is inherited, in a family in Munich, as a strictly dominant sex-linked character (Fig. 108), a type of inheritance which is very rare. Siemens (1925) described this family in which the affected males have keratosis follicularis in the beard, eyebrows and neck, followed by loss of hair, thickening of the skin of the eyelids, loss of eyelashes, ectropion, scarring of the ears, degeneration of the cornea and thickening of the palms and soles.

The females are less affected, and in this sense the condition is incompletely dominant, since they are all (having two X-chromosomes) heterozygous, while the men are hemizygous, having no normal gene to offset the effect of the gene for keratosis. The females have no loss of hair or changes in the eyes, and two of the women who transmitted the condition (I. 2 and II. 2) were doubtfully normal. Siemens thinks the keratosis arose as a mutation, since I. 2 was normal. But since II. 2, who transmitted the condition, may have been normal, I. 2 may also have been heterozygous but normal.

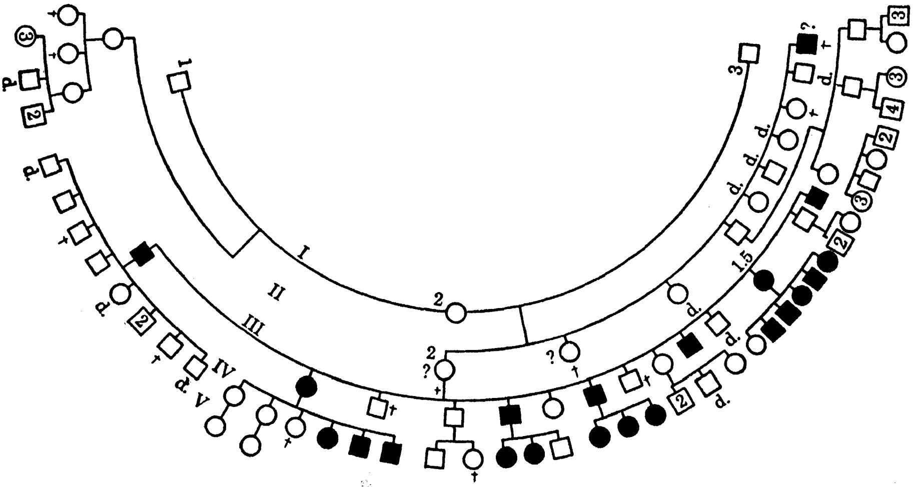

Fig. 108. Dominant sex-linked keratosis follicularis spinulosa cum ophiasi. (Modified after Siemens)

In the inheritance of a sex-linked dominant, an affected man mated to a normal woman will pass his affected X-chromosome to all his daughters, who will therefore all show the defect, but to none of his sons, who will all be normal. In the above pedigree there are three affected fathers (III. 4, 8, 10) who have families with a total of seven sons, all normal, and five daughters, all affected, in accord with expectation. When the mother is affected and the father normal, the expectation is that half the children of each sex will be affected, i.e., a ratio 1 **♂** : 1 ♂ : 1 **♀** : 1 ♀. In the pedigree, four heterozygous mothers (I. 2; II. 2, III. 5 and III. 15) had a total of about 11 **♂** : 8 ♂ : 5 **♀** : 11 ♀ children. As several others died early who might have developed the disease, the results are fairly in agreement with expectation.

Keratosis follicularis spiralis is the name given by Lehr (1939) to a new form of keratosis follicularis. Beginning at about five years of age, on the extensor surfaces of the arms and legs cornification of the hair follicles and subsequent growth of the hairs spirally within the follicles produce pinhead pimples like goose flesh. The hairs persist, forming whitish horny nodules. Pedigree A (Fig. 109), of German and Polish stock, has 25 cases (5 ♂ 20 ♀) in four generations; pedigree B, of Scotch-Irish-German extraction, 18 cases (3 ♂ 15 ♀) in five generations. The condition is dominant, with a great excess of affected females. The author suggests the following hypothesis : the autosomal gene (**F**) for the condition is dominant in females and recessive in males. Then **FF** is an affected ♂ or ♀, **Ff** is an affected ♀ or a normal ♂, **ff** is a normal ♂ or ♀. Hence there will be three times as many affected females as males. The actual number is 37 ♀ : 7 ♂. Two normal males transmitted the condition, indicating low penetrance in the male. In all the sibships only one normal female is recorded.

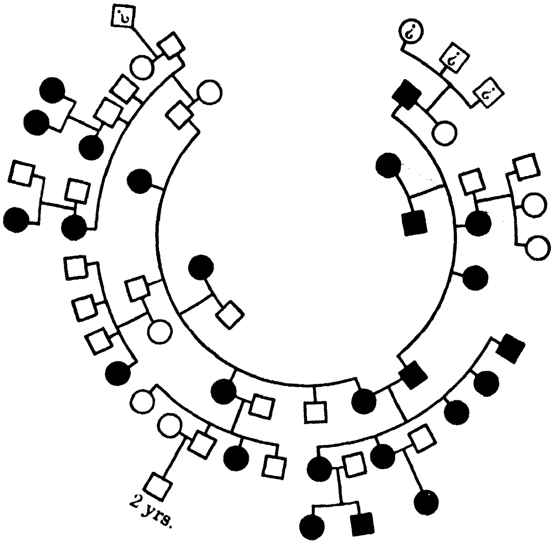

Fig. 109. Pedigree of keratosis follicularis spiralis. (After Lehr)

Monilethrix

This is a rare condition in which the hairs are beaded, and it is accompanied by keratosis follicularis. The babies may be born bald or with normal hair, but when this is lost it is replaced by moniliform hairs, in the follicles of which keratosis appears. The hair in all parts of the body may be so altered or it may be confined to a patch on the head. One man with no moniliform hair and keratosis follicularis only on the occiput and the nape of the neck had children with both conditions well developed. There is thus much variation in monilethrix, but it is accompanied by baldness or thin hair.

Most of the hairs are constricted at regular intervals. They remain short (¼ in. to an inch in length) and break off at the nodes. A few scattered hairs remain normal. The medulla is absent at the constrictions and the follicles show hyperkeratosis at their orifice. The cause of the periodic constrictions is unknown, but in some cases the spindle is formed by day and the constriction at night. Affected persons are usually healthy and not defective. This type of fur is normal in the shrews (Soricidae).

Anderson (1883) described a Scottish family with 16 cases (9♂ 7♀) in five generations of farmers. The condition is a strict dominant, with 14 affected : 20 normal in the sibships. The affected members in this family had dark hair, the normals having a fair or reddish complexion. Hence there is probably linkage between monilethrix and a gene for hair color. In two solitary cases the hair was light. In future studies of monilethrix the hair color of affected and normals should be noted. Tomkinson (1932) recorded another Scottish family, all miners, with 22 cases (15♂ 7♀) in five generations, the sibships 20 affected : 36 normal. As the hair breaks off it scarcely ever has to be cut. The pubic hair is also affected, and keratosis pilaris was also present.

Sabouraud (1892) recorded a French family with 16 cases (8♂ 8♀) in five generations and no skip. Gossage (1908) noted five families with dominant monilethrix, but skipping a generation in one family. Heuck (1924) found monilethrix associated with keratosis follicularis in thirteen out of forty-five cases. The dominance was irregular in some cases. There were five carriers, four of them females, but the proportion of diseased to normal was 47 : 46. Other families are cited by Danforth (1925) in which he shows wide variation in hair shape on the individual.

Two families with dominant monilethrix were recorded by Roberts and Thomas (1930), the K family with 18 cases (6♂ 12♀) in four generations and the I family with 9 cases (2♂ 7♀) in three generations. Both apparently began with a mutation; in the K family a female with six normal sibs and two generations of normal ancestors and collaterals, in the I family a female with normal parents and eight normal sibs.

Cockayne (1933) recorded 15 families with sibships totalling 92 affected : 89 normal; adding 19 less complete pedigrees gives a total of 79♂ : 70♀ affected, so the condition is a simple dominant, generally without a skip, and the sexes are about equally affected. In twenty-one cases there were one or two affected sibs from normal parents. Perhaps most of these are cases of failure of penetrance in a parent, but some may be mutants and possibly some represent a recessive inheritance, although no case of recessive monilethrix has been recorded. Tomkinson (1935) recorded a family in Glasgow with mother and three of six children affected. The condition has been found in English, Scottish, Danish, German, French, Italian, Czech, Russian, Jewish, Armenian, Persian, Arab, Tamil, Singalese, Japanese and Brazilian families.

Ringed hair is a distinct condition described by Cady and Trotter (1922) and first recorded by Karsch in 1846 under the name *pili annulati.* The hairs are cylindrical but banded with light and dark zones owing to the presence of masses of air bubbles (fusi) at intervals in the cortex. In mass the hair appears sandy and speckled. They record three families and found eighteen cases in the literature. Snell and Foley (1932) record another; all are dominant, the last having nine cases in four generations. Ehrhardt (1932) records another dominant family with nine certain and three probable cases in four generations. By shaving a small portion and examining it ten days later, she showed (as did Wilson in 1867) that the light spots are irregular and not related to day and night. Juon (1942) records a Swiss family with eight cases in four generations, dominant.

Nearly related to monilethrix is the condition known as *pili torti* or twisted hairs. The short, broken hairs, appearing in children, resemble the condition of monilethrix. The hairs are not beaded, however, but flattened at irregular intervals and twisted through 180°. The first case was referred to by Schütz in 1900, and cases were reported in 1925 by Ormsby and Mitchell in New York under the name *atrophia pilorum*, by Freund in Italy and Galewsky (1932) in Vienna, who suggested the name *pili torti.* Cases were also observed in France and Germany. Rygier-Cekalska in 1935 observed it in a pair of twins. Touraine (1938) found this very rare condition in a mother and her five children. Hitherto it had only been seen in females, but in this family three of the affected children were boys. The children had no hair until they were a year old, when hairs began to appear, very pale, fine, like little scales on the scalp. Their growth was unequal, being dense on the vertex and occiput, less so on the temples. The hairs are like wool, dry to the touch, and they break off at a length of a few centimetres. They are of two types, (1) reaching 25 cm. long, (2) less numerous, on the top and back of the head and mostly at the front and sides, only 5–8 cm. long, less pigmented, spiral and contorted, breaking easily. There was no axillary, pubic or body hair. Martin (1938) describes a Spanish family with 7 cases (3♂ 4♀) in three generations, irregular dominant.

Hellier, Astbury and Bell (1940) describe the first case in England and review the subject. About 29 cases have been recorded (8♂ 19♀). They studied a typical case in a girl two years old. She was born with very little hair; later it became frizzy and contorted at the sides of the head, the eyebrows being affected in the outer half, eyelashes normal. She was given thallium acetate, which produces complete hair fall, but the regrowth was twisted as before, the hairs being broken, and short, especially over the occiput. There was also a characteristic peculiar spangled glint due to reflection from the twists, with periodic torsions of the hairs. All but two cases have had blond hair, but as the twisted hairs on the same head are lighter than the normal in color, this is probably not a case of genetic linkage between separate genes for twist and pigmentation.

From the work of Astbury and others, it is known that the proteins making up wool and hair fibres are molecularly constructed of polypeptid chains laterally linked at intervals to form grids. It was found that neither in pili torti nor in monilethrix was there any molecular disturbance in the patterns. It has been shown (Wildman) that the crimp of merino wool fibres arises from a twist which is associated partly with the curvature in the hair follicle and partly with rhythmic rotatory movements of the follicle. It is therefore the growth mechanism of the follicles which is at fault in monilethrix and pili torti, and presumably also in twisted and negroid hair generally. In normal hair the axes of the cells and of the keratin chain-molecules are parallel to the axis of the fibre. In pili torti and monilethrix there must be frequent departures from parallelism, leading to severe inter- and intramolecular strains. These may account for the brittleness, but there may also be irregular cross-linkages in the molecules.

Thysanothrix is a condition in which the hairs in some parts of the body grow in a tuft of ten to forty-five hairs from each follicle. The follicles are greatly dilated, with horny plugs at the mouth and hyperkeratosis at the base. A number of single cases have been described, and one probable case in a sister. It is probably a mutation, but more data are required. Szodoray (1939) describes a case and cites the names *thysanothrix* (Franke), *trichostasis spinulosa* or *keratosis spinulosa with trichostasis* (Galewsky) and *lanugocomedo* (Csillag) indicating different aspects of the disease.

Pityriasis rubra pilaris is a rare condition which begins in childhood or early adulthood with a scaly scalp and thickening of the epidermis of the palms and soles, which flake off; large scales also form on the trunk and limbs. Histologically there is universal hyperkeratosis. In many, the health is unaffected, but some families in which the cases are mostly fatal may have a different etiology. The cases described are mostly solitary, but conditions in two French and one German family indicate, according to Cockayne, an irregular dominant heredity for the structural defects or for a susceptibility factor. The condition, which resembles psoriasis, was described by Devergie in 1857. Zeisler

(1923) described four cases, including two sisters. Weiner and Levin (1943) continued the study of Zeisler's family, finding 39 cases (30 ♂ 6 ♀) in three generations. They found that feeding carotene or warmer weather improved the condition. *Pityriasis versicolor* is confined to males but is transmitted by females. Sedgwick (1863) cites a family in which the grandfather, three sons, and nine grandsons were affected.

Porokeratosis, described by Mibelli in 1893, is characterized by hypertrophy of the stratum corneum followed by other changes. It begins with a small circular lesion; this grows and others appear, the development being extremely slow. The lesions develop a raised margin with a white ring and brown pigmentation. They are generally symmetrical and may arise in any part of the body, but in each affected family they tend to occupy similar areas. The disease is found mostly in Italians, but occurs in other Europeans, as well as Hindus, Chinese and Japanese. It is probably most common in Mongolians. Cockayne found 14 families with more than one generation involved, including 90 cases. The sibships number 84 affected : 107 normal. In all reported cases the sex ratio was 136 ♂ : 60 ♀. The condition is a strict dominant, with the male sex much more affected than the female. Bloom and Abramowitz (1943) found 37 further cases reported since 1931. In their family, the father, two sons, and apparently the grandfather were affected.

Verrucosis (epidermodysplasia verruciformis) is an extremely rare condition in which numerous symmetrically placed warts occur on the skin of the face, scalp, trunk and limbs, frequently on the palms and soles. They are oval and grayish-white or yellowish in color. Cockayne found only 9 cases (5 ♂ 4 ♀) described, two of them being Swiss and two Japanese. Beginning in infancy or adolescence, fresh lesions continue to appear, and in three cases they developed carcinoma. The condition may be a dyskeratosis or an infection through the blood stream with the virus of warts. If the latter is the case, there must be a special disposition in those affected. The parents were normal and in two cases consanguineous. There appears to be a recessive inheritance of a predisposition to the disease. Sullivan and Ellis (1939) describe a case in a man of twenty-two, and Wise and Satenstein (1939) record the third case in America, in another man. Loveman and Graham (1941) describe cases of *acrokeratosis verruciformis* of naevoid origin in mother and daughter.

Ichthyosis

This condition of rough, dry and scaly skin occurs in many forms, some of which are still difficult to separate from each other. *Lamellar* *ichthyosis* is an extremely rare condition in which the embryonic epidermis is in two layers, a superficial epitrichium and a deeper layer. Normally, the epitrichium, consisting of large polygonal cells with big nuclei, develops at the second and disappears at the end of the sixth foetal month. In this condition it is retained as a dry, shiny, brownish-yellow collodion-like envelope after birth. Then it peels off and in a few weeks or months the skin becomes normal. Transitions occur between this and the mildest form of ichthyosis congenita. Some seventeen single cases are reported. Auspitz in 1869 reported a family in which the condition was probably recessive. Normal parents had six children, three of them affected. But Dean (1921) described a baby born with the epitrichium. The mother and her sister had both been born in the same condition, so this case was probably dominant.

Ichthyosis foetalis or *harlequin foetus*, which goes under several other names, 'is a remarkable and very rare condition. The child is nearly always born alive but never survives more than a few hours or days. The external ears are usually absent or ill-formed, the nose unformed, the mouth open. The infant cannot suck and dies of starvation or of infection through cracks in its skin. Hypertrophy of the epidermis begins after the third month, causing the lower layers of skin to expand and rupture the outer layers. The thyroids are very small and atrophic. This is regarded as another effect of the same (polyphanic) gene.

There is no sharp distinction between this condition and ichthyosis congenita, and they are probably not genetically distinct. Riecke (1900) reviewed the early literature. A pedigree (Fig. 110) compiled from Sedgwick (1861) shows clearly recessive sex-linked inheritance. Orban-Vadja (1925) recorded a similar case of the disease, transmitted by females and appearing in males. Pick (1925) noted a case of two brothers affected, six other children healthy, the parents unrelated; and Lundborg (1926) described a Swedish peasant family with five cases of recessive sex-linked *ichthyosis simplex* in five generations. A mild form of ichthyosis, with rough dry skin, was shown by the

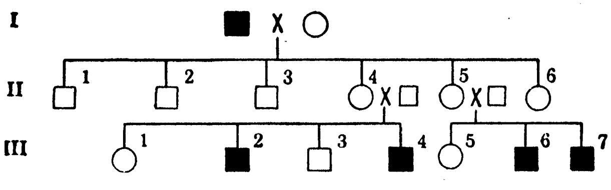

Fig. 110. Pedigree of recessive sex-linked ichthyosis. (After Sedgwick)

pedigree of Manson (1928) to be dominant in three generations. Wehefritz (1924) also gives a pedigree of inheritance as a dominant, but in which a generation may be skipped. Thomson and Wakeley (1921) described two cases and give an excellent discussion of ichthyosis congenita with many illustrations. It was first described in 1792 under the name *cutis testacea.* Simpson suggested the term *ichthyosis intrauterina.* Ballantyne (*Diseases of the Foetus*, 1895) investigated forty-two cases. There is a marked family prevalence and association with consanguinity. The parents are generally free from skin affections. On the hypothesis of Thomson and Wakeley, the harlequin foetus results from hypothyroidism coincident with an anomaly of the foetal thyroid gland. They suggest that this condition and true ichthyosis differ from cretinism because two different isomers of thyroiodin are involved. The common names *armadillo*, *coat of mail*, *bark of a tree* and *tortoise* are all appropriate. Hess and Schultz (1921) gave a fully illustrated description of another case.

Cockayne listed 62 single cases, 31 ♂ : 31 ♀. Although the family histories are very incomplete, the harlequin foetus is clearly a recessive condition; but the sibships number 37 affected : 40 normal instead of 1 : 3. This is because many normals are omitted in families which are unrecognized since, although both parents are heterozygous for the condition, they do not happen to produce a harlequin child. There are few statements regarding consanguinity of the parents. The condition is known in the peoples of Europe, but has not been recorded in colored races. The same recessive defect is found in calves, which die in a few hours or days.

In *Ichthyosis congenita* (Fig. 111) the skin is smooth and shining, deep reddish brown at birth and thick enough to prevent sucking and to cause eversion of the eyelids and limited movements of the limbs. Fissures soon develop in the skin and the infant dies in a few days or weeks from infections. The condition is therefore like delayed ichthyosis foetalis and may be genetically the same. In extreme form the skin is a leathery mail with red, bleeding fissures, and the gene is of course a lethal. That the condition is recessive and lethal was shown by a case of Mohr (1926). A normal woman had five normal children by a normal husband, then three congenitally ichthyotic children by her half-brother.

Siemens divided this condition into ichthyosis congenita *larvata*, in which the lesions are present at birth, and ichthyosis congenita *tardiva*, in which they appear weeks or months after birth, but as both have occurred in the same sibship the distinction is probably not sound. A welter of other names has grown up around the general condition of ichthyosis, but any classification is at present largely tentative. *Keratosis universalis* is another name for ichthyosis congenita. Mullen (1936) described two sibs of *larvata* type (lethal) from normal parents.

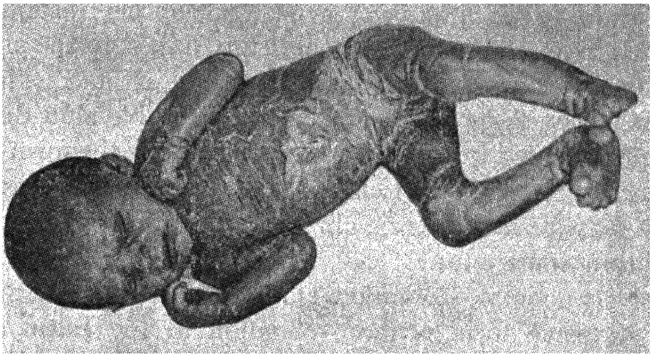

Fig. 111. Ichthyosis congenita in an infant 4 days old. (After Ellis)

West (1937) described a family in Michigan. A man had by his first wife two normal children, both of whom in turn have normal children (Fig. 112). By his second wife he had five children with abnormal skin, the sixth being an infant of fifteen months. The parents were not related and they have normal ancestors. Four of the children have ichthyosis of the *tarda* type and IV. 6 has psoriasis and anhidrosis. Since at least five out of six children are affected, West suggests (on the analogy of the two white varieties of sweet pea which, when crossed, produce color) that two non-allelic genes are necessary to produce the ichthyosis. These children are also shy and backward.

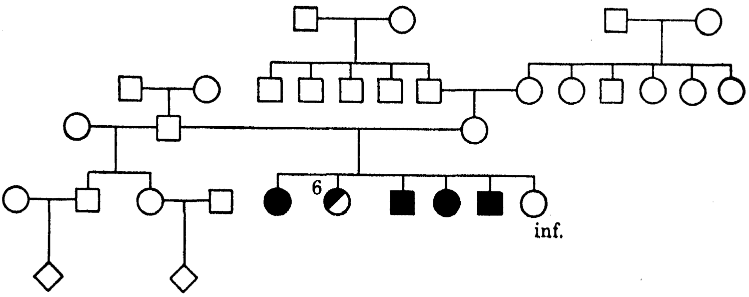

Fig. 112. Pedigree of recessive ichthyosis, perhaps due to complementary genes. (After West)

Ichthyosis vulgaris or *simplex* is the name applied to the relatively benign condition, with smaller scales, which is dominant in inheritance. The scales are continually shed from the dry, scaly skin, especially from the knees, elbows and extensor surfaces. The condition appears in infancy and is fully developed at ten years of age, but the health is unimpaired and it is not connected with hypothyroidism. It often skips one or more generations in some pedigrees. This may be due to the presence of an inhibiting gene. Ichthyosis, although not in itself an allergic reaction, may be genetically linked to the allergic conditions, infantile eczema, Besnier's prurigo and asthma. This connection has long been known. Prurigo is an incurable skin disease with small pale papules and itching. Besnier's prurigo is the form associated with asthma, hayfever and urticaria. The genes for ichthyosis vulgaris and allergy may be in the same chromosome or merely associated (in different chromosome pairs).

Ichthyosis as a simple dominant is found in northern Europe. The sex-linked recessive form is more common in the Latin countries.[3] In seven Norwegian families ichthyosis may be linked with a gene for imbecility. In some other families the affected are nearly all males or nearly all females. This might be due to an inhibiting sex-linked gene, but more information is required. In Japan it is rare and only the recessive form is known (Komai, 1934).

The recessive sex-linked form of ichthyosis vulgaris is clinically indistinguishable from the dominant form. The Hungarian pedigree of Csörsz (1928) shows some interesting features (Fig. 5, p. 12). It includes a marriage between an affected male (V. 2) and a female carrier (V. 1). The children were 2♂ : 1♂ : 1♀ : 2♀, which is as close as possible to the expected ratio 1 : 1 : 1 : 1. The condition was truly recessive since, as generally with color-blindness, only homozygous women showed it. Frets (1929) reported a sex-linked family under the name *ichthyosis generalis*, with four affected males in four generations. Orel (1929) concluded that recessive ichthyosis congenita was a distinct anomaly from recessive-sex-linked ichthyosis vulgaris. He cited a pedigree by W. Boeck of I. vulgaris with mental defect (both ectodermal) extending back to 1680. In the Ramorino (1924) pedigree of sex-linked I. vulgaris (Fig. 113), in the second generation there is a case of direct transmission from father to son, the other nine cases all being, as usual, from affected father through normal daughters to half their sons. Unless this is incorrect, there must have been crossing-over between the Y- and the X-chromosome. Or conceivably non-disjunction might have produced an egg with no X, an X-sperm from the father thus giving rise to an XO son!

In all the recorded pedigrees, the sons of female carriers are 72 affected : 56 normal, where equality is expected. The excess of affected is unexplained, although it might perhaps be partly accounted for by the greater interest in recording an affected than a normal individual. The ratio of carrier : non-carrier females, 54 : 7, is also unexplained, unless a lethal gene is common in the normal population.

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[3] Davies and McGregor (1942) describe a family with eight cases, all females, in three generations. Some also had eczema. This appears to be hologynic inheritance.

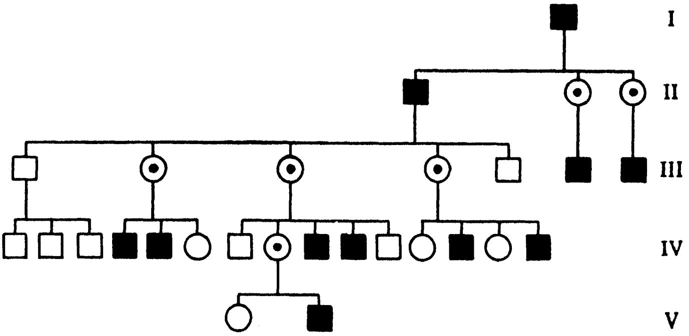

Fig. 113. Pedigree of recessive sex-linked ichthyosis vulgaris. (After Ramorino)

In Cockayne's (1933) pedigree of sex-linked ichthyosis, with four cases in two generations, the distribution of the lesions is different from that of the common dominant form. They are mainly on the trunk and only slight on the face and scalp. In summary, the harlequin foetus is a recessive lethal, ichthyosis congenita essentially the same, while the milder ichthyosis simplex (vulgaris) may be either dominant or sex-linked recessive.

Congenital ichthyosiform erythrodermia or ichthyosis congenita tardiva is not so mild as ichthyosis vulgaris. The skin develops redness and becomes thick and scaly, but the child survives. The keratosis may be slight, or horny plates may form, or spines, and the color may become yellowish, brown, greenish or nearly black. This condition differs from ichthyosis vulgaris in that (1) the flexures of the skin are not more or less normal, (2) bullae frequently appear, (3) there is hyperidrosis (excessive sweating), especially of the palms and soles. In some cases the hair and nails grow very rapidly; in others the hair may be scanty and the nails underdeveloped. Some also have keratosis palmarum et plantarum. The inheritance is recessive. Cockayne's tabulation of 94 full sibships shows 140 affected : 236 normal or 1 : 1.6. If the 17 sibships with 7 or more children are taken, they give a ratio 40 : 109 or 1 : 2.7, while sibships of 8 or more children give 23 : 74 or 1 : 3.2. It is therefore clear that a single gene is involved. This is confirmed by the presence of consanguinity in 32 per cent of the sibships, or 60 per cent if only those are taken where there is full information.

Ichthyosis congenita has been found in various parts of Europe as well as in Turks, Arabs, Sudanese and Japanese, but appears to be most prevalent in the Latin peoples.

There is a dominant form of congenital ichthyosiform erythrodermia, which has been recorded in three families with affected members in two successive generations. The skin is red at birth, keratosis develops later; the hair is scanty but the nails grow rapidly and there is hyperidrosis of the palms and soles.

Erythrodermia exfoliativa universalis congenita is a condition described in six families in which there is continual shedding of thin flakes of skin, new flakes being formed quickly day after day. Only ten cases were known up to 1933, and Wile's pedigree shows the condition to be recessive.

Keratosis palmarum et plantarum with onychomadesis (loss of nails) was described by Azúa in 1892 in a Spanish family. In addition to the keratosis of palms and soles, the ears and nose were red and scaly and the nails were shed periodically. This probably represents a separate mutation, and as it was present in grandfather, father and son it is probably dominant. Keratosis of palms and soles only was dominant in nine pedigrees (Fuhs, 1930). DeBray and Sainton (1930) describe many cases in four generations of a family.

Erythrokeratodermia variabilis is allied to ichthyosis congenita, but with differences in the lesions. Cockayne collected five families with ten cases, all females. The condition is probably dominant, with an excess of affected females.

Ichthyosis hystrix gravior is a unique mutation which appeared in the Lambert family near Euston Hall in Suffolk in the eighteenth century. A country laborer showed his son, then a boy of fourteen, before the Royal Society in 1731. It is probably the most striking mutation which has been recorded in man. The boy's skin, except the palms and soles, head and face, was covered with rough scales. Machin (1733), in his account, says, "The bristly Parts, which were chiefly about the Belly and Flanks, looked and rustled like the bristles, or Quills, of an Hedge-Hog, shorn off within an Inch of the Skin." The skin was clear at birth, but at seven or eight weeks it began to turn yellow, then gradually changed to black, then thickened. The same boy, Edward Lambert, was later shown to the Royal Society again (Baker, 1755). He was now a man of forty with a son like himself and was exhibited in London as the porcupine man. Baker described his skin as like an "innumerable company of warts, of a dark-brown color, and a cylindric figure rising to a like height, and growing as close as possible to one another." These cylindrical projections grew to nearly an inch in length before being shed in the autumn of each year. They were so stiff and elastic that when the hand was passed over them they made a rustling sound. From a drawing of the hand the nails appear normal. A century after the first exhibit, there is a brief reference (Pettigrew, 1833) to an exhibition of the great-grandson at a meeting of the Westminster Medical Society. The story is now that he is descended from an imaginary native of Davis Straits (Eskimo). In the four generations only males were affected, the females of the family being all normal. The back of the hand was "a thickly set brush of horn." Mr. Pettigrew was stated to have said that "numerous births of scaly male children" occurred, but apart from this statement the reporter confesses, "what Mr. Pettigrew said about him we have forgotten." Earlier generations were exhibited on the Continent and studied by various eminent naturalists there. Three contemporary accounts are to be found in Voigt's *Mag. f. Naturkunde*, 1801–02, and Sedgwick (1861) refers to the two brothers of the fourth generation who had seven normal sisters and visited Germany in 1802.

Cockayne (1933) has compiled a pedigree (Fig. 114) from the data available regarding this remarkable family, but there were more affected males than he shows. The pedigree, however, makes it clear that, since the inheritance was always in the male-to-male line, the mutation must have been in the Y-chromosome.

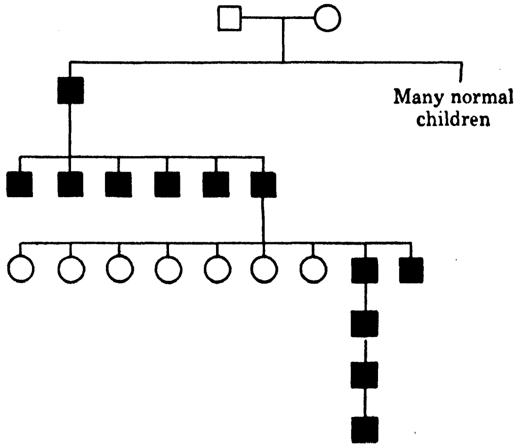

Fig. 114. Ichthyosis hystrix gravior (the Lambert family). (After Cockayne)

A further statement from Baker (1755) is worth quoting: "It appears, therefore, past all doubt, that a race of people may be propagated by this man having such rugged coats or coverings as himself; and if this should ever happen, and the accidental origin be forgotten, 'tis not improbable they might be deemed a different species of mankind: a consideration which would almost lead one to imagine that if mankind were all produced from one and the same stock, the black skins of the negroes, and many other differences of the kind, might possibly have been originally owing to some such accidental cause." Here is an eighteenth-century mutation theory of the origin of human races, but the extreme mutation on which it was founded was destined to disappear. These men are stated to have been strong, athletic and mentally alert, as Tilesius' figure of one of them (reproduced in Cockayne, 1933, and Roberts, 1940) would also indicate. If the six original sons had all left descendants they might have been on the way to forming "a different species of mankind." But mating selection was probably against them and so, like many other extreme mutations, they never got beyond the point of beginning a new population. The manner of inheritance, confining the condition to one sex, also precluded a successful result.

A less extreme form of the same condition (Martin, 1818) was Jane Holden, aged three, whose whole skin except the face was "covered with small scales, or rather warty or bristle-like projections," light brown to black in colour and constantly exfoliated. The condition began at the age of three months. Her mother was the same, except that the neck, breast, and forearms, as well as the soles of the feet, were free from this condition. Her parents were healthy, and she was the only one of six children having the disease. In this family, unlike the previous one, the condition is therefore not male-sex-linked.

It is now recognized that *pellagra*, which was known in southern Europe in the eighteenth century as an endemic disease affecting the skin and spine, is a vitamin-deficiency disease, due to lack of nicotinic acid (vitamin B_2 or G) in the diet. Nevertheless there are clearly inherited constitutional differences in susceptibility to the disease. Pellagra was known in Italy long before it was recognized or studied in southern United States, and Lombroso in 1898 spoke of a very severe and a very mild type of hereditary pellagra. Sedgwick (1861) quoted Italian statistics among the peasants of Lombardy. In 184 families there were 671 healthy individuals and 648 showing pellagra, so that differences in susceptibility probably exist within the family. In the years 1912–14 a Commission of the New York Medical School studied pellagra, especially in Spartanburg County, South Carolina. The resulting reports [4] are instructive as showing the

[4] *Arch. Int. Med.* Vol. 18. 1916.

difficulties in unravelling the inheritance element before it was known that pellagra was an avitaminosis disease.

The symptoms of pellagra are recurring inflammation (erythema) and ulcerations of certain skin areas, often symmetrically placed, with diarrhoea from ulcers of the intestines, and often with nervous and mental symptoms as well. Thousands of cases still occur in southern United States and some other parts of the world. Davenport (1916), although he thought the disease was communicable, concluded that its course depends on certain constitutional, inheritable traits of the affected individual. He found that when both parents are susceptible at least 40 per cent of the children are susceptible, although less than 1 per cent of the population have pellagra. This high family incidence was regarded as due to infection whereas it is partly due to similar food habits and partly to inherited susceptibility. Davenport also showed that families differ in their reactions, some never showing mental symptoms while others usually do; some families having slight and others severe intestinal symptoms with early death; some with slight skin eruptions, others with severe ulcers and desquamation. He collected thirty-eight pedigrees showing these conditions. Muncey (1916) collected twenty-seven pedigrees extending through three or four generations and containing, in one family, as many as sixteen cases of pellagra in three generations. Gastro-intestinal symptoms were common in some families for several generations. The nature of the susceptibility factor and the exact manner of its inheritance still require elucidation.

Siler, Garrison and MacNeal (1916) found that while poverty and poor diet were important factors in pellagra, negro pellagrins die much more promptly than white pellagrins, indicating a racial difference in reaction to lack of nicotinic acid. The negroes had a lower incidence rate and a higher death-rate than the whites. Bloom (1931) reviewed the literature of juvenile pellagra, pointing out that inherited constitutional traits probably render the child susceptible.

An inherited susceptibility factor is also important in leprosy and poliomyelitis (*q.v.*) and in other diseases. Many other instances of inherited constitutional or racial differences in susceptibility to particular diseases have been cited elsewhere (Gates, 1942).

Leprosy

Leprosy is one of the oldest recorded diseases and in ancient times was the most feared. The Book of Leviticus contains instructions to the priests concerning what may be regarded as primitive methods of disinfection of a house in which lepers had lived. In the Middle Ages, for fear of contagion, lepers were forbidden to join any company of people, their use of water supplies was severely restricted, they could not touch anything they wished to buy, even a hedge or bush by their pathway could not be touched without gloves; indeed, the rules corresponded closely with those that a modern sanitarian might adopt.

Then, in 1848, Danielssen and Boeck replaced the age-old theory of contagion by the erroneous view that leprosy itself is transmitted by heredity. Their views were based on studies of its familial aggregation in an isolated and sparse focus in Norway. Before this, however, it had long been widely recognized that heredity played an important part in connection with leprosy. Simpson (1842) a century ago, in a sketch of leprosy in Britain in the Middle Ages, recognized the "hereditary transmission of leprosy." He says, "Few facts in the history of tubercular leprosy seem to be more universally admitted by all writers on the disease, both ancient and modern, than the transmission of the predisposition to it from parents to offspring." He cites the leper hospital at Funchal, Madeira, in 1825 with cases of two brothers and an uncle; a leper and aunt; a mother, brother and sister; and a father, mother, three sisters and two brothers in a family who died of elephantiasis. In only three cases was no hereditary taint known. He states that the predisposition may occasionally show in only one or two members of a family and may "lie dormant" for one or two generations, to reappear later. "In the few districts of Europe in which cases of the disease have continued to linger down to a late period, the malady seems to be transmitted through an old hereditary taint in particular families, rather than generated by existing external circumstances active on the bodies of those who now become its victims." In corroboration of this point of view, which is amply confirmed by recent work, he cited cases in southern France and the Shetlands, and states that this heredity was "well known to our forefathers."

Simpson's point of view apparently continued until the discovery of the Hansen bacillus in 1874, which led many to the assumption that leprosy was only a matter of infection. It is only now beginning to be recognized that leprosy is a matter of susceptibility as well as infection by the bacillus, and that the susceptibility is inherited. It has now become clear that constitutional or racial differences in susceptibility are involved in many bacterial infections. The conception of balance and variation between both attacker and defender is so well established in connection with many fungal diseases of plants, that it is difficult to understand how, with the rise of human bacteriology, the possibility of inherited variations in the defense mechanisms of the body was so completely ignored.

Partial acceptance of the argument that since contagion was proven heredity was disproven, is shown by an account by Thin (1892) of the origin and spread of leprosy at Parcent in Spain. A leper came to a neighboring town from the Philippines in 1850. There had been no previous lepers but one man from Parcent got the infection through intimate contact. In 40 years there were about 60 cases in this small village, 45 had died of leprosy, neighboring towns were infected, and in 18 towns of Alicante province there were 154 lepers in an area of 24 square miles. Thin nevertheless described a family (Fig. 115) with 8 cases of leprosy (4♂ 4♀) in five generations, from which it would appear that the susceptibility is dominant. Case III. 1 transmitted the susceptibility but did not contract the disease. The ancestors of III. 4 were free from leprosy and he, being susceptible, presumably contracted it from his wife. If both were heterozygous for a dominant susceptibility factor, one-quarter of the children might be expected to be homozygous for it. This evidence is of course insufficient to determine the genic nature of the susceptibility. Thin also quotes from Dr. Codina's report recommending not only precautions against contagion, such as the wearing of shoes and gloves, but also that lepers should not be allowed to marry because of the inheritance. He himself thought that contagion alone was involved.

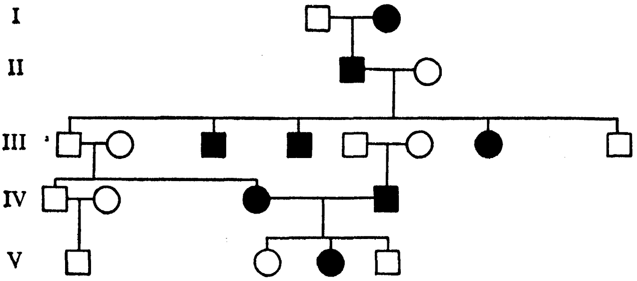

Fig. 115. Pedigree of a family at Parcent, Spain, showing leprosy. (After Thin)

Aycock (1941), in an important paper, shows that leprosy exhibits a definite tendency to restriction in family lines. Its failure to follow the ordinary lines of contagion was attributed to supposed differences in the degree or duration of exposure. There is no question of its spread through contagion, although the incubation period may be very prolonged; but the striking tendency to familial occurrence makes it appear that the result of exposure is determined largely by hereditary influences. It is now recognized that leprosy, while much less frequent than in the Middle Ages, tends to remain restricted to certain regions, races and families for long periods. But hereditary susceptibility has been ignored and a theory of "predisposing causes" has been developed to include anything from puberty to malaria, hookworm, climate, humidity or even laziness. Statistics show that of 178 wives living with leprous husbands from three to twenty-seven years, only 4 contracted the disease. Most persons must then show strong resistance. While there is only 3.8 to 5.1 per cent of conjugal infections, in the children of lepers the incidence of infection ranges from 7 to 44 per cent.

The racial and geographical distribution of leprosy is of much interest. It has been endemic in China for two thousand years; and in Iceland, where it has existed for centuries, there were 226 cases in 1896. Aycock has made an analysis of its occurrence in certain areas. It persists among the Acadian French in New Brunswick and in Louisiana; among the Germans in Galveston, Texas; among a few Norwegians in Minnesota who brought it from Norway; and at Key West, Florida. The California focus came from the Orient. Five out of six cases in Saskatchewan were in the Dukhobors from southern Russia, the sixth being a Syrian. It is endemic in Argentina, Paraguay, Brazil and Colombia.

The history of this disease in New Brunswick and Louisiana is especially significant as showing how important is the susceptibility factor. The French of New Brunswick and Louisiana came from a common source at the time of the expulsion of the Acadians from Nova Scotia in 1755, and they have many of the same surnames. There is no record of leprosy among the Acadians of that time, and probably both groups have since been independently infected in these two localities, one north temperate, the other subtropical. The first case in New Brunswick was that of a woman in 1815 whose grandfather came from St. Malo, Normandy, where leprosy existed. Since then, 300 cases have been recorded, all from a few villages on the Gulf of St. Lawrence coast where they were much interrelated. In 14 families there have been 252 cases. Leprosy was found among the Acadians of Louisiana as early as 1766. In 1933 there were 471 cases in the State, 391 of them born within the State. The case furnishes evidence of the racial, regional and familial occurrence of leprosy.

The little island of Nauru in the South Pacific, with a population of 2200, half native and half imported labor, had, in 1922, 35 lepers, 34 of them natives, with a high degree of consanguinity. Leprosy among the Australian aborigines shows similar familial concentration of the disease. Huizenga (1942) shows that in China for over two thousand years leprosy has been confined mainly to six limited areas.

At the sixth Pacific Science Congress, fifteen papers were presented on leprosy. In one of these, Lowe (1942) shows how the disease varies in different countries and races. There are mild and severe forms, which he concludes are due to differences in susceptibility. The disease is milder in India and Africa, more severe in Burma, Siam, China, Japan, the Philippines and possibly South America. In Malaya there were marked differences in the form of leprosy in Indians, Chinese and Malayans. These differences must be racial rather than climatic. There might be an acquired racial immunity, but it is much more likely that racial differences in resistance to the disease exist.

In relatively immune races, the immunity is most marked in adults, so that most cases are acquired in childhood. In relatively susceptible races the disease progresses rapidly before adulthood and prevents marriage. The severe type of leprosy also tends to produce sterility. Badger (1942) thinks that in Hawaii racial and family susceptibility appear to play no role, the incidence depending on contact with infection and on individual susceptibility. Rats on a diet deficient in vitamin B_1 are more susceptible to rat leprosy, so that diet probably also affects human susceptibility. There is some evidence that allergic factors may also play a part in the pathogenesis of leprosy.

Epiloia was the name given by Sherlock (1911) to a syndrome of sebaceous adenoma (Pringle type), epilepsy, mental deficiency and brain tumors (tuberous sclerosis), leading to idiocy. A butterfly rash of the nose and cheeks is characteristic. It was first described by Bourneville in 1880. The main features are tumors of the skin, with hyperactivity of the sebaceous glands of the face and areas of sclerosis in the brain. Epilepsy may appear a few weeks after birth, other mental changes only in adult age. Tumors may also appear in the kidneys, heart and other viscera. Neuro-fibromata as well as pigmentation and depigmentation of the skin can also occur in epiloia as in von Recklinghausen's disease. The syndrome is often incomplete. It may begin with a sebaceous excretion at the sides of the nose in the fourth or fifth year. Some patients attend dermatological clinics, others come before a psychiatrist, neurologist or a heart or kidney specialist.

Fuhs (1925) recorded it in a family under the name *naevus multiplex* (Pringle). There were 12 cases (8♂ 4♀) in five generations, three of them without cerebral sclerosis, the inheritance dominant. Brushfield and Wyatt (1926) and others have described families showing the variable symptoms. The adenoma sebaceum can occur without brain tumors, and the tuberous sclerosis without skin tumors. It is essentially a tendency to the formation of particular kinds of tumors, and has been found in Nordics, Mediterraneans, Slavs, Jews, Chinese, Japanese and Negroes. Cockayne listed 15 sibships with 33 affected : 55 normal. The affected were 43♂ : 31 ♀.[5] The gene is probably an irregular dominant with variable expressivity in the heterozygous state. The homozygous condition is unknown, but would quite possibly be lethal. Gunther and Penrose (1935) recorded twenty family histories from institutions. They estimate that it has a mutation rate of 1 in 120,000 to 1 in 60,000, with a frequency in the population of 1 in 30,000. The rare dominant gene may be accompanied by modifiers.

In a later study, Penrose (1936) points out that epiloia can occur in three degrees: (1) So mild as to pass for normal (due to the presence of modifier genes). (2) Only one of the three, brain — skin — viscera, symptoms may be present. (3) Severe, when two or three of these systems are attacked. In fourteen families both parents were normal, but probably in seven of them near relatives had the disease. In three other cases a parent was severely affected and in three a parent was mildly affected. Penrose assumes the presence of three modifiers, f_1, f_2, f_3, for normal, mild and severe. These also affect fertility. It is found that 0.7 to 0.8 per cent of idiots and imbeciles have epiloia. For every twenty-four severe cases there are theoretically forty more due to mutation. This would give a mutation rate of 1 in 40,000. An uneven distribution of modifiers would explain why there is a much higher proportion of sporadic than of hereditary epiloia among idiots. Lichstein and Solis-Cohen (1943) describe two cases, in one of which epiloia appears to be an irregular dominant in the family. X-ray photographs showed calcifications in the brain, which produce the epileptic seizures. Denny-Brown (1938) described a mother and two sisters with adenoma sebaceum and a son with epilepsy, none having complete epiloia. Good and Garb (1943) describe a woman of twenty with naevoid growths in a butterfly arrangement on the face, tuberose sclerosis (tumors scattered in the frontal lobes, cerebellum, medulla, spinal cord and retina) and a fibroma from mesodermal tissue on the scalp. Her father and three of five sisters had abnormal electroencephalograms (see p. 1097).

Epidermoid cysts or *atheromata*, also known as *sebaceous cysts*, occur from the size of a pea up to that of a hen's egg on the scalp and sometimes on other parts of the head, neck and body. They generally develop between twenty and thirty years of age, but rarely number more than a dozen and often not more than two or three. Paget in

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[5] In this and other references to Cockayne in this chapter the two numbers of affected do not agree because the first refers only to sibships while the second includes all recorded cases.

1853 regarded the cysts as more commonly inherited than cancer. The condition has been inherited for as many as ten generations, and can be transmitted by an unaffected male. In Bauer's (1919) pedigree, with 17 cases (9♂ 8♀) in four generations, it is strictly dominant and combined with leuconychia. Siemens (1923) cited 11 cases (4♂ 7♀) in four generations of one family and only three cases in four generations of another. He collected 34 familial and 75 single cases from the literature. In 30 of the 34 families the cysts were localized in the scalp; in one case the onset was congenital, in three others in the seventh decade of life. There was no evidence of inheritance of follicular cysts. He believes that *dermoid cysts* are a different thing, as they are extremely rarely inherited. Ingram and Oldfield (1937) describe a family with 5 cases (3♂ 2♀) in three generations, strictly dominant. The cysts may occur on the scalp, face, legs (Fig. 116) or the palms, where there are no sebaceous glands or hair follicles. E. Wilson (1937) records another family. Cockayne listed 41 families with 97 affected : 195 normal, 71 ♂: 66♀. The large excess of normals in this condition, which is dominant with a few skips, may mean not only low penetrance but perhaps an inhibitor in the population as well. It has already been recorded in English, Germans, French, Italians and Japanese, so that, like other mutations, it may be assumed to have arisen more than once.

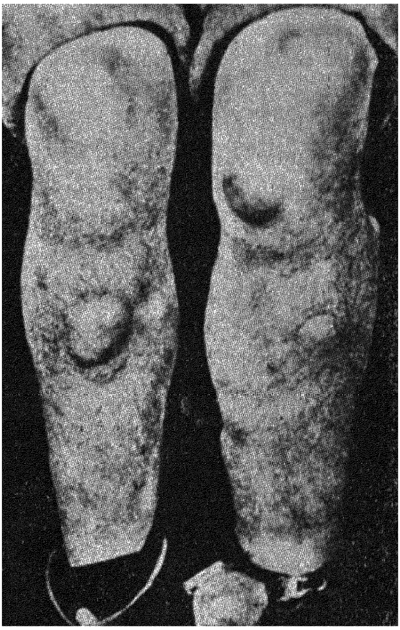

Fig. 116. Multiple sebaceous cysts. (After Ingram and Oldfield)

Levit (1931) described a Russian family in which soft sebaceous cysts on the scalp only were inherited recessively. Two affected parents had three children, all affected. The son took a wife from an adjacent village, who was probably heterozygous though normal. They had five affected and five normal children. The five affected (sons) married normals and had a total of twenty-five children and seven grandchildren, all normal. If the condition were dominant, half of these twenty-five children should have shown it. Sedgwick (1863) found the condition sex-linked in two families. Munro's (1937) family produced twenty cases in four generations, dominant with three skips. The wens or cysts were seven times more numerous in the

B and C branches than in the A branch of the family, which is ascribed to the presence of modifiers in the A branch. In a family in which both parents were affected, three of ten children died in infancy (two in convulsions). They may have been homozygous (and lethal) for cysts. It is clear that sebaceous cysts are usually dominant, but that in occasional families they are recessive or sex-linked. Levit thinks they result from an abnormally narrow sebaceous gland duct. There is a possibility that they may arise through a virus infection.

Sedgwick (1863) recorded two families in which the inheritance was clearly confined to females. In one, all the females who attained the age of ten years were affected, and no males were affected. There must have been at least twelve cases. The other family showed the same inheritance for five generations. As a possible explanation, we may assume that in both these families the two X-chromosomes of the females were joined end-to-end ($\widehat{XX}$), producing non-disjunction. But as the joining or non-disjunction of the chromosomes cannot be expected to produce the gene, it is evident that, if this explanation is correct, there should also be pedigrees in which the same condition is inherited as a simple dominant or recessive sex-linked character. We have already seen that such pedigrees exist. In Sedgwick's families, however, the condition is transmitted by normal males, so this is not hologynic but sex-limited inheritance. Cockayne (1933) assumes that XXY individuals would be abnormal intersexes, XXX and YY non-viable. While this is true of *Drosophila melanogaster* with only eight chromosomes, it is not necessarily true for man with forty-eight. One extra chromosome would be expected to produce much less disturbance in the human germplasm.

Pilonidal sinus is a dermoid cyst or sinus in the sacro-coccygeal region, containing hairs and often opening at a postanal dimple. These sinuses have been recognized for nearly a century. They constitute an inherited embryological defect. Kooistra (1942) studied 350 cases, finding the frequency to be about 1 in 940 persons. In about half the cases the lesion contains hairs. They are almost restricted to Caucasians and 74 per cent are in males. They are unknown in Mongolians, rare or absent from American Indians and rare in Negroes. They develop an abscess and frequently require treatment at about twenty-five years, but may recur after operation. This congenital anomaly probably arises very early in embryonic life and appears to be most common in persons with an excess of body hair. Kooistra records the condition in (1) a father and two sons, (2) two brothers and a sister, (3) two pairs of identical twins, (4) two cousins. It was found seven times in two brothers. Although clearly inherited, the method of inheritance appears somewhat irregular. Walker and Bucy (1934) described seven cases and suggested that the sinus is due to a failure of the cutaneous and the neuro-epithelial ectoderm to separate, the neural tube carrying down a pocket of skin and so forming a cyst. Whyte (1938) gives an account of the literature and theories of the condition. It probably occurs equally in both sexes.

In *benign cystic epithelioma* there are usually many small cysts on the face, ranging in size from a pinhead to a split pea, while on the scalp they may reach the size of a walnut. They generally begin at puberty, but have no malign symptoms. They have been recorded from many parts of Europe, but are less common in Negroes and Mongols. Small pedigrees show the condition to be dominant, but more frequent in females. Cockayne found 51 ♂ : 80 ♀ in sibships and 32 ♂ 58 ♀ as isolated cases. Bovero (1929) noted the occurrence of free *sebaceous glands in the mucous membrane* of the mouth and cheeks, quite frequent. They occurred more often in men than women; in 72 per cent of Negroes and 56 per cent of whites. They were more numerous and polymorphic in Negroes, in whom they may be considered normal.

Acne and *seborrhoea* are related conditions of the sebaceous glands. In acne, which exists in many forms and may have allergic connections, the skin, especially of the face, breaks out in pimples, particularly at puberty. Erasmus Darwin referred to its inheritance in 1797. Stokes and King (1932) published five pedigrees of acne vulgaris and concluded that the predisposition is hereditary. Its incidence in the parents of patients was twenty-six times that of other parents, and probably involves the element of polygenic susceptibility. Persons with *seborrhoeic dermatitis* show a family history of atopy in 28 per cent, as against 13 per cent for those with acne. Siemens (1926) studied acne rosacea and related conditions in twins. He found that in 36 pairs of MZ twins they showed great similarity, whereas 12 pairs of DZ twins nearly always showed marked differences. He suggested a polyhybrid inheritance. In addition to a genetic factor causing the development of large and active sebaceous glands, infection by a microorganism may be necessary. Siemens (1930) examined twins with *seborrhoeic dermatitis*, an inflammation of the skin. Among 43 pairs of MZ twins, both had it in 22 cases and only one in 21 cases. Among 32 pairs of DZ twins, both had it in only 8 cases and one in 24 cases. There is probably an inheritance factor and it may be dominant, but infection by an organism is also involved. Seborrhoeic families are common enough, but certain families appear to be almost immune. Barber (1929) quotes Scholtz, who defines the seborrhoeic diathesis as a congenital or hereditary tendency to show certain clinical skin manifestations under the influence of certain dietetic and metabolic factors. Of two persons under the same conditions, one may become seborrhoeic, the other not. Jews are notoriously liable to seborrhoeic manifestations as well as diabetes. Excess of alcohol also promotes seborrhoea.

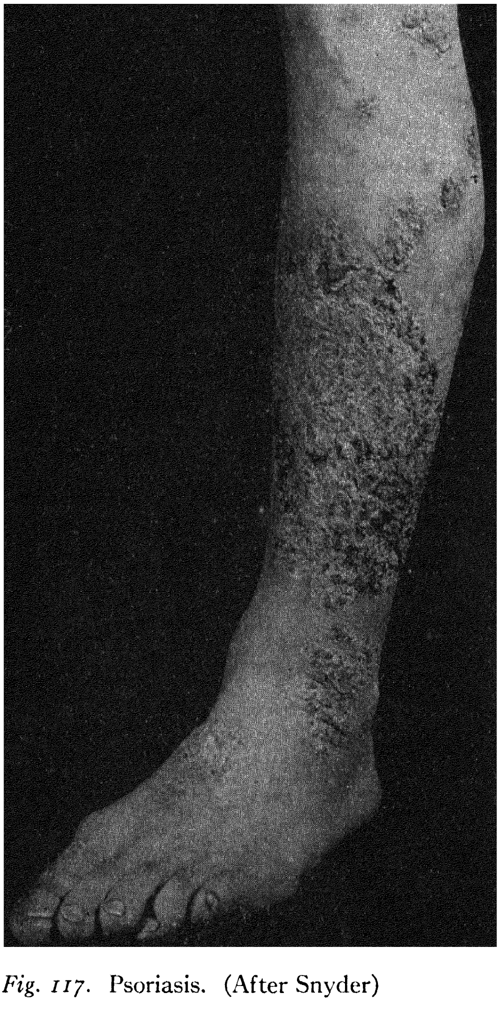

Fig. 117. Psoriasis. (After Snyder)

Ford (1940) described a condition like acne, but more severe, in natives of Papua and north Australia. It was first seen in Papua in 1915. Pustules appear on the nose, spreading to the face. They leave scars but disappear spontaneously after many years. Even the uvula and palate may be affected.

Psoriasis (Fig. 117) is one of the most common skin diseases, in which red scaly patches appear on the extensor surfaces of the arms and legs. It was known to the Greeks. It occurs in many varieties and the suggestions regarding its causation include (1) toxins in the blood, (2) nervous origin, (3) allergic manifestation, (4) a metabolic disorder, (5) an infection, (6) mechanical irritation. There is some evidence of contagion, but no organism has been found. The condition generally begins at puberty or later, but may appear in infants or as late as sixty. Schamberg (1924) reported on 592 private patients, finding multiple cases in 13 per cent of families and only two cases in which husband and wife were affected. Hecht (1930) collected thirty-two pedigrees and concluded that men only are affected in some pedigrees, transmission being by the females, but that it is generally recessive and rarely dominant. Heiner (1926) published four pedigrees in which it is an irregular dominant, with ten cases in four generations of one family. The sibships showed 34 affected : 29 normal, and 63 per cent of the afflicted were males. It often skips a generation. Cockayne tabulated 14 families with 81 affected : 125 normal, the sex-ratio being 54♂ : 42♀, or with the conductors (7♂ 10♀), 61♂ : 52♀. Snyder (1941) published a dominant pedigree with seven cases and a recessive one with four cases.

Leven (1928) published two pedigrees of psoriasis, (1) with 10 cases (4♂ 6♀) in four generations, (2) with 5 cases (3♂ 2♀) in four generations, both strictly dominant. Marcuse (1929) described a Jewish family in Berlin with psoriasis and gallstones. The psoriasis is dominant, with thirteen cases and one skip, the cholecystitis an irregular dominant, with seventeen cases and five skips. Six persons had both afflictions, but they are probably independently inherited. Weber (1933) described twin sisters with *psoriasis arthropathica* (with stiffness and swelling of joints). The parents were normal and another (among nine sibs) had psoriasis from two years of age, but with very little effect on the joints.

Riebler (1936) described a family in Innsbruck in which the mother, two daughters and a son had psoriasis, endemic goitre, obesity of cerebral-hypophysis nature and neuropathy; the father and another son were neuropathic. He concludes that in psoriasis there is an inherited constitutional anomaly. The son with psoriasis had also gynecomasty, neurasthenia and exophoria. Weber and Lauber (1939) described four cases with direct inheritance through four generations (♀–♂–♀–♀). In the last generation it was only in the axillae, the mother had it on elbows and knees, her father had it "all his life."

Psoriasis is most common in Iceland, where it constitutes 50 per cent of all skin diseases. In England it represents 7 per cent. It occurs in the European races, Jews, Chinese, Japanese, Malays, Hindus and Polynesians, but is rare in Negroes and mulattos. Gahan (1943) finds it more frequent than any other skin disease. He estimates its frequency in the white population of New York at 1 per cent or more.

Adamson (1935) finds some evidence that psoriasis is an allergic manifestation. Spindler (1933) has a pedigree with 19 cases (13♂ 6♀) in four generations. The ancestors were all normal for nine generations back, most of them converging on one couple. He finds that the frequency in families ranges from 5 to 50 per cent, and concludes that the inheritance is dominant, but trauma, infection, endocrine or other disturbance is required to bring it out. Lerner (1940) has a pedigree with 8 cases (3♂ 5♀) in four generations, dominant with three skips. He studied 172 private cases and confirmed the usual inheritance as an irregular dominant.

In *Schaumann's disease* or *Boeck's sarcoid*, red patches occur on the arms, legs and face and develop slowly with pulmonary symptoms.

Dressler (1938) described it in two brothers and MacCormac (1939) in two sisters.

Multiple rodent ulcers are a distinct type, brownish red with the edges rolled up. The embryonic pilo-sebaceous follicles or the sweat glands are probably not properly developed and retain the power of proliferation. Only eight cases were recorded. Gray (1920) found the condition in two brothers, the father and one brother also having psoriasis. McFeeters (1939) described seven cases in a family — the mother and six of eight children (in four of them on the ear).

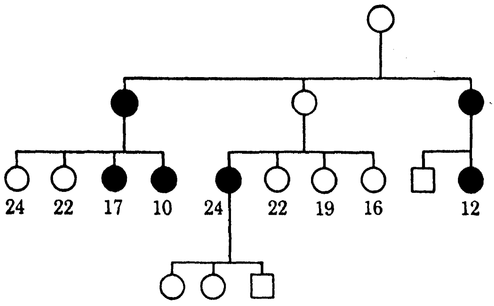

Fig. 118. Cyclical ulceration of the buccal and genital mucosa. (After Pappworth)

The condition may be recessive with the father a carrier. *Cyclical ulceration* of the buccal and genital mucosa, with seven cases (all females) in two generations of a family is described by Pappworth (1941). After the menopause the ulcers recurred every four weeks; previously they appeared for two or three days before and after each period. The inheritance is sex-limited (Fig. 118). It was first described by Neumann in 1895 and fifty cases have since been recorded, but in only nine is there mention of the relation to menstruation. This condition is probably more common than generally supposed. Lipschütz first described recurrent ulceration of the vulva alone in 1913. He afterward reported fifty-one cases, in only one of which were buccal ulcers present. Recurrent ulceration of the mouth alone is common, but there appears to be no evidence regarding its heredity.

Poikiloderma atrophicans vascularis is a very rare condition, usually occurring in single cases. The child's skin is rough and scaly, with later a livid reticulation of the skin, with pigmentation, atrophic spots and telangiectases. It has been recorded in two brothers and in three sisters. This and other evidence shows it to be recessive. Heggs (1936) cites a son of normal parents with poikiloderma and an extra thumb on both hands. The same condition of poikiloderma and recessive radial polydactyly was present in a cousin from marriage between the father's sister and the mother's brother. The two conditions are probably linked.

In *urticaria pigmentosa* numerous wheals develop on the body in crops, then retrogress, leaving brown macules which later disappear. Little collected 154 cases (86♂ 52♀) in 1905. They were mostly single cases but included, (1) two brothers, (2) two sisters, (3) three sisters, (4) two sibs, (5) a patient, the mother and cousin, (6) a pair of identical twins aged five months. This shows inheritance, but the method is not clear, although probably recessive.

Keloid is an overgrowth of connective tissue in the dermis, causing atrophy of the outer layers of skin and projecting above the surface. Keloids may begin from an injury or spontaneously. They are commoner in negroes than whites and some African tribes take advantage of their relative susceptibility to form cheloid patterns (wheals) on their skin. Cockayne recorded 8 families with a total of 11 affected : 14 normal members, 13♂ : 14♀. The condition is dominant in whites, one family having five cases in three generations. Garb and Stone (1942) describe and illustrate eighty cases of keloids, mostly produced by trauma. They suggest an endocrine constitutional cause.

Aplasia cutis congenita generally takes the form, in infants, of one or two circular patches of hairless skin over the posterior fontanelle. They may correspond in position with the fenestrae parietales (*q.v.*). Very rarely this condition may affect the dorsal aspect of the hands and feet. Dowling (1930) described two sisters with congenital red patches of atrophic skin in this position.

Much has been written on the inheritance of *naevi* or moles, and *birth-marks*. In a pedigree of Meirowsky and Bruck (1921), seven individuals out of eleven in three generations had a particular birth-mark, inheritance dominant. Meirowsky and Leven (1921) made a classification of skin markings and naevi. Birth-marks have been regarded from the earliest times as indicating relationship. Siemens (1924) studied 45 pairs of MZ and 27 pairs of DZ twins, classifying the naevi as (1) flat or unpigmented, (2) vascular. The 45 pairs all had naevi, which averaged 18.5 per person. They differed in position and number but showed greater similarity in the MZ than in the DZ pairs. Lenz (1926) studied three hundred pairs of twins. In the case of pigmented naevi (mostly liver-colored spots) the coefficients of similarity were consistently *ca.* 0.8 for MZ and 0.4 for DZ twins. Siemens did not allow for the fact that naevi increase during childhood and youth. By excluding this age effect, Lenz obtained slightly higher frequencies. They conclude that naevi are inherited but not as a simple dominant. *Unna's naevus*, a flat, capillary naevus at the nape of the neck, is shown by these studies to be inherited. More recent work indicates dominant inheritance with an occasional skip. Denaro (1944) cites numerous cases indicating a tendency to inheritance in the same part of the body in many pedigrees. Certain types of naevi show some relation to cancer.

Naevi are of many kinds and are often the starting point for melanotic tumors.[6] *Melanoma of the choroid* probably originates from a group of naevus cells. In one family, a mother, two of her sisters, her daughter and her father were all affected and had an eye removed. In another family, two brothers had melanoma of the eye. It is well known that gray horses develop melanoma of the hairless, pigmented parts of the skin. *Naevi spili* or *N. pigmentosi* occurring in large numbers are more definitely inherited. They are congenital spots of melanin pigment which remain smooth and unaltered. Solger reported such a naevus on the forehead near the midline in grandmother, mother and daughter. Leven records naevi on the neck and both cheeks in a mother and two daughters. Estabrook (1928) records a family with 9 cases (6♂ 3♀) in five generations (Fig. 119). In III. 2, III. 7, IV. 6 and IV. 9 it was near the navel. In III. 9 and IV. 11 it was a large spot on the neck, back of the left ear. They extend in size and get darker during the growing period, but there is evidently some inheritance of location. *Naevus flammeus*, a port-wine stain of the skin, is common and is directly transmitted in some cases. Such facial birth-marks are known, since 1860, to be associated with glaucoma and sometimes with other ocular defects (Stoll, 1936; Mehney, 1937, Evans, 1939). Meirowsky (1942) has a fully illustrated study of the

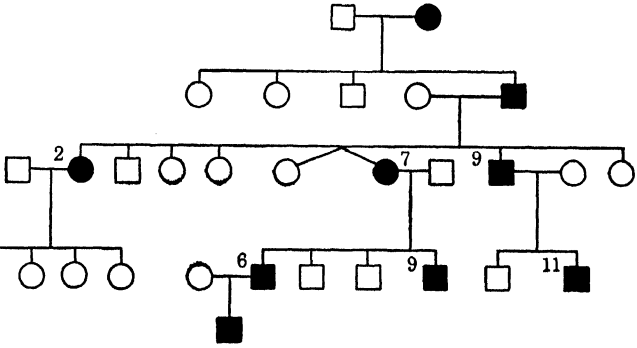

Fig. 119. Inheritance of naevus spilus. (After Estabrook)

inheritance of moles and naevi, with two pedigrees. Corson (1934) described *naevus flammeus nuchae* (Unna's naevus), a mild form at the nape of the neck. He found it in 5 per cent of 760 persons examined, including a mother and daughter. It is probably a common simple dominant.

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[6] Nordby (1933) described the inheritance of melanotic skin tumors in pigs. They looked like warts or pigmented moles. A boar with such a "wart" on his loin produced ten or more young with warts, by various sows which probably carried the factor, as the condition appears to be recessive.

Brauer (1929) described a Dutch family with 38 cases (24♂ 14♀) in five generations of *naevus aplasticus* as an irregular dominant with six skips. There is an area above the outer part of each eyebrow, running up to the temple, where the skin is depressed, smooth, hairless and yellowish or brownish in color. The sensation was normal and the condition could be unilateral or bilateral.

Wile and Duemling (1930) described two sisters with the same distribution of *xanthoma*. *Pseudoxanthoma elasticum* is a condition with symmetrical lesions of the skin, the elastic tissue being affected. The skin takes various colors and the lesions may occur in the neck, axillae, groins and elbows. Ten families were reported, with 4♂ and 13♀ cases; the condition is probably recessive, with a large excess of affected females. It has been reported in Irish, English, German, French, Italian and Japanese. A closely related condition is recorded in three families of Danes and Norwegians, in which there are firm, raised whitish-yellow lesions on the chest with a hair in the centre of each. Lack of elastic tissue is shown histologically and it is probably dominant in inheritance.

A peculiar abnormality of skin color was reported in a Russian boy and girl, sibs with fair hair and skin, by Wende and Bauckus (1919). At one year of age, pigmentation began in the scalp and hair, face and trunk, the face and trunk finally becoming almost black. Partial depigmentation processes led to variegated coloring ranging from white to yellow, brown and blackish. There were many chromatophores in the corium.

Acrokeratoma is the name applied by Neuberger in 1891 to a condition, first recognized by Mibelli in 1889, in which the whole skin, the nails, conjunctiva and mucous membrane were brownish-yellow, the skin rough and sprinkled with violaceous nodules containing yellow fluid. The nails were thick, the hair scanty, no sweat and no subcutaneous fat. In a German family there were three affected males in three generations, so the mutation was probably dominant. Pringle (1913) described such a family with telangiectases or warty growths in groups and thickening of the epidermis chiefly on the feet and legs of the children. A man and his three sons were all affected. Under the name *acrokeratoma hystriciforme*, Tommasoli described a young woman whose mother and grandmother had the above defect more strongly. Beginning at puberty, the skin became wrinkled, harsh, dry and dark, with black horny excrescences on the hands and over the joints (like ichthyosis hystrix). The horny layer of the epidermis was enormously thickened.

Maleda is a little island on the Dalmatian coast, whose population is closely intermarried. They were supposed to have leprosy, but the condition which has been known for over a century proved to be an inherited skin abnormality, now known as *Mal de Maleda*. Siemens called it *keratosis palmo-plantaris transgrediens* and found seventy cases. In 1930 there were still twenty-one cases. Those affected show keratosis of the palms and soles with hyperidrosis. It differs from tylosis in having hyperkeratosis also on the back of the hands and feet, the knees and elbows and sometimes on the forearms and legs. From the pedigrees of Neumann it appears to be dominant, but as the gene is frequent in this inbred population it may be recessive. A similar condition described in France, in which the teeth were also defective, is definitely recessive. A case in an English girl, with symmetrical keratodermia on the hands, forearms, knees, ankles and feet, is very similar.

Tylosis palmaris et plantaris (also known as *ichthyosis* or *keratosis palmarum et plantarum*) is a condition in which there is great thickening of the palms and soles, generally with hyperidrosis. The middle layer of the stratum corneum is most thickened, but those affected do not experience inconvenience. Bloom's (1931) Greek family had 12 cases (6♂ 6♀) in four generations, strictly dominant. Cockayne lists 47 families with 594 affected : 483 normal. The condition is dominant, with 318♂ : 284♀ affected. In Hahn's pedigree there were 27 cases (12♂ 15♀) in five generations, strictly dominant. One marriage was between two parents, both affected (heterozygous). They had four affected children and one normal. The two who had children were both heterozygous (having a normal child). One of the others might have been homozygous, but if so the condition must be completely dominant in the heterozygote. In several cases the tylosis may have originated *de novo* by mutation.

Hanhart described a Swiss family in which the affected members developed tylosis at fifteen and multiple lipomata at twenty-two years of age. There were five cases, all males, in three generations, and these two conditions are probably closely linked, but the tylosis develops much later than usual. Jacob and Fulton (1905) published a pedigree of tylosis with 14 cases (7♂ 7♀) in five generations. The original woman was probably a mutant and all her twelve children were affected. This is Gossage's (1908) version of the pedigree which, as Cockayne states, is probably the correct one. It is very rare, however, for an original mutation to be homozygous, and not readily accounted for. A similar, but early, case of a homozygous hexadactyl mutation is recorded on p. 416. Both members of a pair of somatic chromosomes would have to undergo the same mutation. Gossage cites another family with 7 cases (3♂ 4♀) of tylosis in four generations and one of Thost (1880) with 15 cases (10♂ 5♀) in four generations, all dominant with no skip. In an English family with five cases in four generations and a Brazilian family with cases in three generations the condition was limited to the female sex and occasionally skipped a generation.

A family with keratosis palmarum et plantarum and short, broad hands was recorded by Thatcher (1912) on a small island in the Shetlands. The normal parents, who were related, had three of five children affected, so this is probably a recessive.

Tylosis plantarum, in which only the soles are affected, was observed in a grandfather, father and son. It could be dominant, but the boy had twelve normal sibs. *Keratodermia palmaris*, with only the palms thickened, was described in two brothers with normal parents (Crawford, 1922) and may be recessive. *Keratosis palmarum et plantarum without hyperidrosis* was described in seven families, mostly French, but one Polish and one Negro — a simple dominant. In the variety *striata* the thickenings tend to take a linear arrangement. Five families are recorded, the condition a simple dominant, but with much variability which may be due to modifiers. In *keratodermia maculosa* horny papules develop on the skin of palms and soles. Fourteen families were recorded, with 34 affected : 42 normal, the affected 25♂ : 21♀. One case originated *de novo* by mutation.

Keratoma dissipatum is the name applied to a condition which is clinically indistinguishable from the last (hard, horny papules develop on hands and feet), but the inheritance (in three families) is holandric. Brauer (1913) gives a pedigree of nine cases (all males) in two generations. As the original parents were normal, the mutation in the father's Y-chromosome must have occurred early in his germplasm. His nine direct male descendants in two generations were all affected. In the third generation there were eleven sons, all too young to develop the lesions. In Junghanns' (1922) family the condition appeared in the males of three generations. In another family, normal parents produced three affected sons and four normal daughters. In the third generation the sons produced six grandsons, all affected, and one normal granddaughter. The females of the second generation, on the other hand, produced eight sons and four daughters, all normal. Hence the inheritance was clearly in the Y-chromosome. Unna's type of keratoma of palms and soles is dominant (Günther, 1932). Michael (1933) reports a family in Texas with six generations of dominant *keratoderma dis-*

seminatum of palms and soles, 33 cases (15 ♂ 18 ♀) and only one skip. The papules arise around the sweat glands. Whether the diffuse and striate forms of keratoderma represent separate genes or are an example of heterophenism (Siemens) is uncertain. The papular form is less intense than the diffuse and appears later (about eighteen years of age).

Keratoma mutilans is a form of keratosis leading to spontaneous amputation of certain fingers near the base. Several families with dominant heredity have been described, and one mutant. The condition may be the same as *ainhum*, which is widely known in Negroes of West Africa, West Indies and Brazil, but has not been regarded as hereditary.

In *erythema palmare* the palms are bright red and sharply demarcated, probably through dilatation of the capillaries. Lane (1929) described it in two families: in one, a boy and girl were affected, and a sister normal; in the other, the father, son and daughter had red palms, eight sibs were normal and the son had five normal children. It is probably an irregular dominant. Several other cases were reported in the discussion.

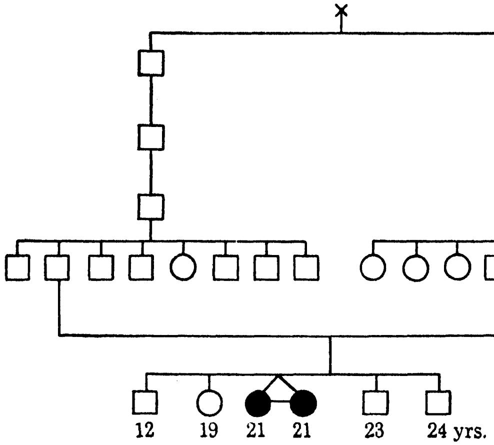

Fig. 120. Hereditary eczema. (After Mayr)

There are many varieties of *eczema*, a condition with local burning, itching and vesiculation of the skin. Some forms are congenital and one form is an expression of allergy. There is frequently a constitutional factor, but it has been very little studied. The earlier dermatological literature gives strong indications of the hereditary character of eczema. E. Veiel, in 279 cases of chronic eczema, found inheritance in 112. Also in several sibs or twins circumscript eczema, especially of the seborrhoeic sort, in different locations and with different morphology, gave indications of heredity. Mayr (1935) described a case of identical twins, twenty-one years of age, who are descended from a common ancestor five generations back (Fig. 120). At twenty-one months they both had a crustaceous rash on the head, which remained for three years. In the second year it spread to the body, where it remains in varying intensity, especially in spring and autumn and at menstruation. The inheritance is evidently recessive and he suggests that several genes are required for its production. These twins had the same heredity and the same environment, with a like weakness. The relation of eczema to constitution merits fuller study.

Ectodermal dystrophies of the skin take a wide variety of forms, each specifically inherited and each affecting teeth, hair, nails, sweat glands or other structures of the skin more or less profoundly. Those mutations in which the teeth are mainly affected will be considered in a separate section.

Hypertrichosis universalis, hypertrichosis lanuginosa or "dog-faced" men is a very rare condition in which the face and body are clothed with hair. The ears are generally hairy at birth, while facial and bodily hirsuties begin at two to seven years. The hair continues to grow until the body and face, except the palms and soles, are covered with long, silky, silvery gray or pale yellowish hair which may become 8 to 10 in. long. The dentition varies from an almost complete lack of teeth to only two or three missing. A full account is given by Danforth (1925), who states that probably not more than thirty families are known, and Cockayne (1933). One family lived near Innsbruck about 1600. The mother was normal, the father, son and three daughters hairy. In another family in Basle about the same time the father, son and daughter were hairy. A celebrated Burmese family (Crawford, 1854) began with a dog-faced man who was said to have had normal ancestors. He had four children. Two died young, the third was normal and the fourth, a daughter, was hairy and had two hairy sons (Youle, 1858). The affected were born with hairy ears. The incisors were present, the canines and molars absent, and the hair developed at one year or five years. A Russian family in 1828 consisted of father, son and daughter with hypertrichosis and few teeth. A Polish family near Warsaw consisted of father and son, the grandparents being normal. From the few other recorded cases it is clear that this very rare dominant condition has arisen as an independent mutation several times in different races. That it has any atavistic significance is doubtful. Von Luschan (1907) estimated that a new case occurs about once in a thousand million of population. Liu (1937) describes another case in China. It is curious that the least hairy (Mongolian) race shows this mutation most frequently. Danforth (1925) gives a great deal of other information on the inheritance of hair conditions.

Hypertrichosis terminalis with simian features has occurred twice in parent and child. There is a persistent growth of lanugo, and long black hair covers the body, irregular teeth and a simian face completing the syndrome. One case was that of Krao. She was born in Tonkin and brought to Europe at the age of six years. The other was Julia Pastrana, the dancer, born in Mexico of normal parents. In 1860 she gave birth to a son like herself. Lesser degrees of hypertrichosis in men can be observed on any bathing beach. Redlich (1926) noted cases of men with the back and shoulder covered with hair, others with hairy chest and still others with markedly hairy legs. Studies of the inheritance of these conditions are needed. Lehmann-Nitsche (1914) described a man of German, Italian and Bohemian descent who was very hairy on the breast and abdomen. His parents and four grandparents all had full head-hair in old age.

Excessive growth of the beard or moustache has sometimes been recorded. Allworthy (1909) noted the case of a man with a remarkably luxuriant beard. He rolled it up in a pad as a chest protector, but his throat and chest suffered and he died in consequence at sixty-four. The beard at one time measured 130 in. in length, although at times he had to cut off considerable portions which became unmanageable. Beigel (1868) relates the story of three similar cases: (*a*) the burgomaster of Braunau in 1572, whose beard reached the ground and he was killed in mounting his horse when his beard caught in the stirrup; (*b*) a Hungarian soldier in the Turkish war, who could cover his whole body with his beard, like a mantle; (*c*) a carpenter whose figure stands in the courtyard at Eidom, who rolled up his beard in a bag while at work. He cites other cases of hypertrichosis.

A condition of *local hypertrichosis* of the forehead and neck was reported (Boas) in some Indians in British Columbia. The women had hair two to three cm. long here, only a small triangular patch near the glabella being free. In South American Indians a less extreme condition is reported, hair covering all the sides of the forehead. Lusha (1923) cites a Czech family in which hair covered the forehead and all the way down the spine. A girl, her father and both his grandfathers were the same. Hershan (1927) finds a hereditary type of hypertrichosis in women, affecting the beard, arms and legs but independent of hormone action.

Hypertrichosis of the eyebrows (as heavy as a moustache) in a father and one son was described by Monteiro (1921), and hypertrichosis of the eyelashes in a father and two of his daughters (Marquez, 1928). Michelson (1885) recorded a family (Fig. 121) with missing teeth, mostly upper incisors, in some members and hypertrichosis of the chest, shoulders and back in others. Some also had hairy hands, nose and ears. The head hair was very thick and the eyebrows bushy.

The text states that there were five affected males in generation III. The original ancestor had both the hypertrichosis and the missing teeth, the genes for which are evidently in separate chromosomes.

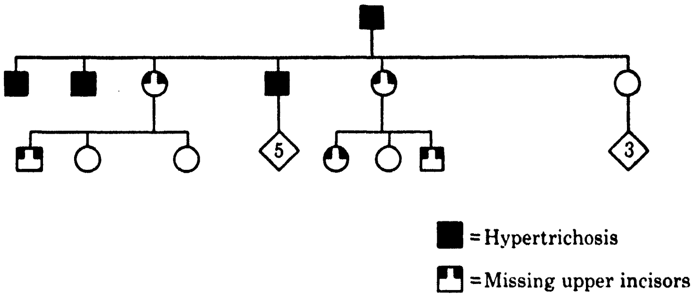

Fig. 121. Pedigree of missing incisors and hypertrichosis. (After Michelson)

Trotter and Danforth (1922) made a study of *facial hypertrichosis* in women. It has generally been regarded as a result of endocrine disturbance, but there is little evidence for this, and it appears to be due to germinal factors controlling the amount of hair. Out of 350 women college students, 94 (26.8 per cent) had facial hypertrichosis. It was found that colored women and insane women showed about the same frequency of hypertrichosis, and it is not associated with reduced fertility. As regards inheritance, since the condition cannot be recognized in the male, its statistical frequency in the female was calculated on the assumption of a dominant factor being concerned, and this gave results in accordance with the observed frequency. In a study of 29 cases of hirsutism in females, Bissell and Williams (1945) found in the majority no endocrine derangement and considered these "iodiopathic." Twenty-four had a heavy beard which required daily shaving, twenty-three had the male pubic hair distribution, eleven had an enlarged clitoris, while some showed obesity or menstrual abnormalities, and one was a case of pseudohermaphroditism. Hormones from the anterior pituitary, adrenals, thyroid and gonads are known to affect hair growth, and hirsutism in the female is often associated with disease, especially neoplastic, of these organs.

Danforth (1921) has also made an investigation of the distribution of *hair on the digits* of man. Complete absence of hairs from the middle segment of the digits is a recessive trait. It is a useless character, yet widespread. The evolutionary tendency to lose the hair from the terminal and middle segments of the digits is present both in man and the anthropoids. Man alone has lost all hair from the terminal segments. The inheritance was studied in 80 families with 178 children. With the exception of five children in two families, no child exceeded the degree of digital pilosity of the more hairy parent. The progressive phylogenetic loss of hair from the digits appears from these observations to be brought about by one or more recessive genes, or a main gene with modifying factors, of which sex may be one.

In a recent study of mid-digital hair, Bernstein and Burks (1942) have extended Danforth's study. They find no difference in sex-incidence at ages below eighteen years. A drop in frequency in females after this age is regarded as due to housework. The Irish are found to have less mid-digital hair than other north Europeans, Italians still less and Negroes least of all. Danforth's finding that a child will generally have mid-digital hair on no more fingers than its more hairy parent is confirmed. The authors offer a multiple allele hypothesis, $\mathbf{A}_0$, $\mathbf{A}_1$, $\mathbf{A}_2$, $\mathbf{A}_3$, $\mathbf{A}_4$ (in order of increasing dominance), the subscripts corresponding to the number of fingers with mid-digital hair, $\mathbf{A}_0\mathbf{A}_0$ corresponding to absence of such hair. There is phenotypic overlapping between $\mathbf{A}_3$ and $\mathbf{A}_4$.

Pili incarnati is a condition in which the hair follicles of the beard are oblique, so that the hairs grow into the skin again, forming pustules. There are often two or three hairs in one follicle. It is believed to be very rare, but may have been overlooked. It occurs in the Nordic, Egyptian, Semitic and Negroid races. Three affected brothers were described in one Nordic family (Weninger, 1928). The condition is of course sex-limited and may be recessive. The teeth and nails are normal.

Baldness exists in different forms and may be combined with more or less complete hairlessness of the body. Dorothy Osborn (1916) tabulated the results for twenty-two families showing ordinary early baldness and concluded that the condition is inherited as an autosomal dominant character (**B**) from father to son, being recessive in women, who can transmit it but are only bald when homozygous (**BB**) for the gene. This difference in the sexes is no doubt associated with the different sex hormones, which in turn depend on the presence of one X-chromosome or two.[7] Men and women who are **BB** will be bald, **Bb** men will be bald but **Bb** women will not. The character is inherited in the same way as horns in some breeds of sheep. One of Osborn's four pedigree charts (Fig. 12, p. 27) shows in four generations three cases of baldness in women, as well as fourteen cases in men, some of the others having thin hair (T). Case III. 10, who had very thin hair, was evidently a carrier. Her husband was bald, so the mating would be **Bb** × **Bb**. The expectation is 3 ♂ : 1 ♂ : 1 ♀ : 3 ♀ and the actual numbers of children 4 : 2 : 1 : 1. That there is some irregularity in dominance in females is shown by II. 5, who was **Bb**, in very poor health and much older than other members of her family when baldness appeared. Case II. 9 also had thin hair and would be **Bb.**

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[7] That sex hormones are involved is indicated by the fact that observations in Eastern harems show that a eunuch never develops the male type of baldness.

Snyder and Yingling (1935) produce further pedigree evidence showing that a normal woman can transmit baldness from her father to her son and (Fig. 122) that when both parents are bald all the sons and half the daughters will be bald. They also make a useful analysis by the gene-frequency method, which may be briefly stated here.

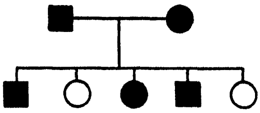

Fig. 122. Inheritance of baldness. (After Snyder and Yingling)

If p = frequency of **B** and q = frequency of **b** in the population, so that $p + q = 1$, XY being the sex chromosomes, then with random mating the offspring and their frequencies will be as in Table 12.

TABLE 12

INHERITANCE OF BALDNESS

♂ gametes ♀ gametes	$\frac{p}{2}$ **BX**	$\frac{p}{2}$ **BY**	$\frac{q}{2}$ **bX**	$\frac{q}{2}$ **bY**
p **BX**	1. $\frac{p^2}{2}$ **BBXX**	2. $\frac{p^2}{2}$ **BBXY**	3. $\frac{pq}{2}$ **BbXX**	4. $\frac{pq}{2}$ **BbXY**
q **bX**	5. $\frac{pq}{2}$ **BbXX**	6. $\frac{pq}{2}$ **BbXY**	7. $\frac{q^2}{2}$ **bbXX**	8. $\frac{q^2}{2}$ **bbXY**

Square 1 contains all the bald women, square 8 all the non-bald men, their respective frequencies being $\frac{p^2}{2}$ and $\frac{q^2}{2}$. Now the proportion of bald women in the population will be half the proportion of baldness among women, or $\frac{p^2}{2} = \frac{\text{bald ♀♀}}{2}$, and $p = \sqrt{\text{bald ♀♀}}$. Similarly $q = \sqrt{\text{non-bald ♂♂}}$, so that $\sqrt{\text{bald ♀♀}} + \sqrt{\text{non-bald ♂♂}} = 1$.

Nearly four thousand inmates of the Ohio state hospitals for the insane (over thirty-five years of age) were examined for baldness, the frequency being .4296 ± .007 for males and .0775 ± .004 for females. In the general population the frequency of baldness in men was essentially the same,

.4050 ± .023. From the above values $p = .278$, $q = .755$ and in the equation $\sqrt{\text{bald ♀♀}} + \sqrt{\text{non-bald ♂♂}} = 1.033 \pm .009$, showing the correctness of the hypothesis.

Fantham (1924) described a Transvaal family with early baldness, all the men (nine in three generations) becoming prematurely bald with the same pattern, while the women have abundant hair. In the grandfather the onset of baldness was at twenty-one, in all the others at about eighteen, with rapid loss of hair above the level of the ears. This might be due to a gene in the Y-chromosome, but it is more probable that women also transmit the condition. In any case, the condition may be nearly sex-limited rather than sex-linked. The gene is autosomal and the difference in the sexes probably results from the great difference in activity of the sebaceous and sex glands. This is well shown in a case described by Barber (1929). A female patient developed a tumor of the suprarenal cortex; she grew a beard and moustache, developed amenorrhoea, with loss of scalp hair like male baldness. After the tumor was removed she developed menstruation, the hair fell from her face and regrew on her bald scalp. This shows the remarkable extent to which the sex hormones have control of hair and skin characters.

Baldness may also be associated with progressive decrease in the concentration of thyroid in the blood. It is no doubt more common in some races than others, and appears to be less frequent in primitive peoples. Jenness (1928, p. 104) observed a single Eskimo in the Coronation Gulf region who was bald. He had a seventeen-year-old son who was nearly as bald as his father. There were no infectious diseases and the condition must have been inherited. Fantham (1925) observed a South African family of English descent with a *small bald spot* about an inch across over the left ear. There were ten cases in three generations. It occurred in both sexes and was a simple dominant, except that in one case it skipped a generation.

Duerden (1918, 1919) showed that in crosses between the North African and South African ostrich the bald spot on the head of the former behaves as a simple dominant character, not sex-limited. In the chicks the head is covered with a bristly down, but in the North African birds this gradually falls out during the first few months and is not replaced by feathers. Sturkie (1941) studied a recessive gene with incomplete penetrance in fowls, which produces bald areas. In ten-day embryos blebs filled with fluid appear over the cerebral hemispheres and the eyes. They form between the dermis and epidermis and prevent the downgrowth of the latter which is necessary for feather formation. The separation of the layers of the skin is due to defects in the epidermis.

Many studies relate to the quantity of hair on particular parts of the body. Hypertrichosis and hypotrichosis are both inherited, as well as alopecia (complete loss of hair). The human races differ in the hairness of their bodies, the Negro having little hair, the Mongolian probably even less; the white races have a considerable quantity, with wide variations in the amount on chest and back. The inheritance of these differences has been little studied, as yet; the Ainu probably have the most hair of all. In a little-known work on the hair of mankind, Friedenthal (1908) gives descriptions with numerous colored plates showing the distribution of hair on the human body, and the extremes of plus and minus variation in various races of man and some apes. Ainu are figured, in some of which almost the entire body has a hairy covering. It is probable that sexual selection as well as hygiene played a part in decreasing the primitive hairy coat of mankind, especially in the warmer climates. This and many other features argue for the evolution of the Negro race under tropical conditions, the white race in temperate regions and the Ainu in the subarctic. The relatively hairless Eskimos would then be descended from Mongolian ancestors who evolved in a warmer climate. It is evident that life under arctic conditions, or those of Magdalenian Europe, was impossible until man learned the use of clothes. The Ainu appear to have been the only possible people in a cold climate who for clothing made their skin do.

Alopecia congenita or hairlessness can of course be produced by disease. When inherited, it may be dominant, recessive or sex-linked in different families. Gossage (1908) recorded seven families in which the children are born hairless or the hair is lost in the first few months of life, the condition being dominant, with twenty-six affected members. Danforth (1925) cites a dominant pedigree from Linzenmeier with nineteen cases in five generations. In Fischer's (1910) Bollenbach family near Colmar in Upper Alsace, the affected members were almost devoid of hair, their nails were defective and their teeth decayed early. The inheritance was probably recessive, if two cousin marriages in later generations are assumed. The two antecedent generations were normal although they involved cousin marriages. The abnormal section of the family was dying out, as the affected members generally remained single and only two old men were left. Their death would extinguish the abnormality after the occurrence of fifteen members in three generations, except in so far as it is still carried recessively in other members of the family. Sobajima (1927) described a Japanese family in which alopecia was inherited as a sex-linked recessive, with twenty-nine affected males. The hair was absent at birth or fell out between the first and third years. While there is no sharp line between alopecia and hypotrichosis, the former term should be confined to the more extreme degrees of hairlessness.

A Punjab Mohammedan family in Burma (Fig. 123) had three members, all males, who had complete alopecia except for a few downy hairs on the head and in the armpits (Sein, 1936). They perspired freely and there were no nervous or endocrine disorders. The condition is clearly recessive and might be sex-linked, but the sisters of the affected men did not transmit it. Oliver and Gilbert (1926) described another of the many forms of alopecia. In two brothers with normal ancestors it was associated with *keratosis pilaris*, which apparently prevented the hairs coming through the scalp.

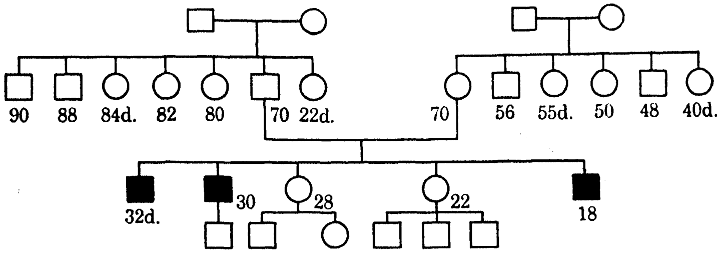

Fig. 123. Pedigree of hairless family in the Punjab. (After Sein)

Featherless pigeons (Cole and Owen, 1944) is a mutation recessive to normal. In fowls, nakedness is a sex-linked semilethal recessive.

Alopecia areata is a condition of baldness in patches, leaving the scalp white. It was formerly supposed to be due to infection but is now regarded as a trophoneurosis arising from abnormality in the sympathetic nerve supply to the skin or its blood vessels. There may also be a toxic or psychic factor involved. Cockayne listed six families with 13 affected : 24 normal. A dominant gene is probably involved, together with an environmental factor to account for the large excess of normals, and both sexes are equally affected. As those affected are stated nearly always to have dark hair, there may perhaps be linkage between this gene and that for dark hair.

Trénel and Prieux (1930) studied a family with congenital alopecia and cataract, but independent genes were involved. The dominant cataract (three cases in three generations) came from the mother's family and was combined with total alopecia in one of her daughters. The alopecia was an irregular dominant on the father's side, with 8 cases (3 ♂ 5 ♀) in four generations. The children were born with hair, which disappeared in the first few months. The eyebrows were blond and a few soft hairs remained on the head; axillary and pubic hair was present and the teeth were normal. One child combined total alopecia with bilateral cataract.

Thorner (1940) records a woman with total loss of hair, of two years' duration. A sister lost her hair in spots in childhood, with spontaneous return later. The parents were unrelated and the condition is attributed to endocrine unbalance. Gillespie (1937) found four sibs out of five with recessive congenital alopecia totalis, the parents related; and Brain (1938) a family with 4 cases (1♂ 3♀) of very thin and scanty scalp hair in three generations.

Alopecia or hairlessness occurs in many mammals, including horses, cattle, goats, dogs, pigs, rats, mice (domestic and Peromyscus), rabbits and guinea pigs. The corresponding featherless condition is known in fowls (dominant), turkeys, parrots, canaries and pigeons. Various incompletely featherless conditions are known in fowls, in which certain pterylae only are involved, as in the bare-neck breed.

In a herd of Holstein-Friesian cattle in Wisconsin, Cole (1919) described a condition in which certain incisor teeth were lacking or deficient, so that grass could only be cropped with difficulty, and the hair was very short, especially on the neck and head. Five calves of this recessive type appeared. Mohr and Wriedt (1928) gave a full account of practically complete hairlessness in Swedish Holstein-Friesian cattle, due to a sublethal recessive gene. By tracing back the pedigrees it was shown that a bull imported from Friesland in 1902 was heterozygous for hairlessness. This condition became widespread in the breed. The calves, which die a few minutes after birth, have a smooth, glossy skin. There are hairs on the muzzle and around the eyelids, the ears are normally covered, but there are few hairs elsewhere. The hoofs and teeth are normal. The condition of the skin was due to a marked delay in its embryonic development. The sweat glands were greatly enlarged, while the development of hair was only about to begin.

David (1932) compared hereditary hairlessness in mammals. A case in mice (*M. musculus*) was described in 1850. Dominant hairless (**Nn**) retains patches of hair in the heterozygote and is lethal soon after birth in the homozygote. The recessive hairless condition (**hrhr**) is found in the house mouse, in Peromyscus, the rat (*M. Norvegicus*) and the rabbit. The teeth are normal in all except the rabbit but the nails of hairless mice are hypertrophied. In the rabbit there is partial agenesis of the hair follicles. In the house mouse, Gates and Pullig (1945) find that the gene for hairless is linked with that for dominant white spotting.

The hairless Chihuahuan dog of northern Mexico is described (*Journ. Hered.*, VIII. 519). It is rare, is very sensitive to temperature changes, and is said to have defective teeth. Hairless × normal gives, at least in some cases, half of each type. Naked dogs have also been known from Ceylon, Turkey and Africa, the hairless condition being dominant. Hairlessness has been reported at various times in different species of mice. Sumner (1924) described the hairless mutations which appeared in breeding experiments with different stocks of Peromyscus. The skin is usually corrugated in folds, and they usually die young. Fifty-two hairless descendants were obtained. In crosses the condition was a simple recessive, but there was a deficiency of hairless due to their lesser viability. Hairlessness in rats, due to a single recessive factor, is recorded by E. Roberts (1929). A practically hairless male wild rat mated with the backcross offspring from an albino female gave in all twenty-two hairless offspring, the hair falling out after twenty-four days.

Hairless rabbits, again a simple recessive, are described by Kislovsky (1928). They appeared from inbreeding normals and were recognizable at about two weeks of age, DR × DR litters giving 17 normal : 7 hairless. Usually there was hair only on the muzzle, tips of the ears, the back of the legs, and a tuft behind the scapula. Some had defective and some normal teeth, but all died before they were a month old; so the condition was lethal and they could not be bred. In pigs (Welch, 1917) the conditions appear to be different, and the kind of hairlessness accompanied by goitre which occurs in them is due to an enlarged thyroid which is deficient in iodine. This condition, which occurs in pigs, lambs and calves in goitrous regions of the northwestern United States, can apparently be prevented by feeding iodine during the period of gestation.

In fowls, the bare-neck breed was described by Davenport (1914). It is a simple dominant mutation, in which the neck pteryla and certain other parts of the skin are devoid of feathers. Davenport suggested that an anti-enzyme inhibitor is present which prevents the development of the enzyme normally causing feather-formation. Crew (1922) has further described these hackleless fowls, and Greenwood (1927) points out that the apteria are devoid both of feathers and also of the down and semiplumes which are found on the apteria of normal fowls. The bare skin of the neck is also thickened and congested with blood vessels, like the comb and wattles. This type is known from Transylvania and also from Barbados. Danforth (1928) applies the term *alopecia* to absence of feathers. In Rhode Island Red fowls a hen appeared with almost full feathering on the head and upper neck, the rest of the body showing deficiency, there being only a few wing feathers, the sides of the body bare, and the tail rudimentary. A piece of skin grafted from a Leghorn produced feathers, indicating that the nakedness was not due to lack of endocrines.

Mid-dorsal hair whorl, with reversal of the hair streams lower down, is apparently rare in Caucasians. Fenner (1942) described a single case. Wood-Jones found it in 61 per cent of pure Australian aborigines in Victoria, Gray in 43 per cent of Central Australians, and Wood-Jones in foetuses of mixed descent from Hawaii.

Hypotrichosis is a related condition which occurs in several distinct forms. There are at least two dominant forms and probably more than one recessive type. The dominant forms (*hypotrichosis universalis*) are: (1) with hyperidrosis (one family); (2) with more or less hypertrophied sebaceous glands. Berglund (1924) recorded a family with 6 cases (4♂ 2♀) in two generations; (3) alopecia with defective nails (Pinkus); (4) hypotrichosis with defective nails (to be described below); (5) hypotrichosis with small sebaceous glands (Hanover family of Unna); (6) with increase of hair at puberty (two families); (7) alopecia affecting only the scalp (two families). These seven types all differ in certain respects. They are all strictly dominant. In relation to each other they may be different genes (some perhaps alleles) or they may represent a single gene with modifiers. Henckel (1935) described identical triplets (Fig. 124) and a cousin descended from two cousin marriages. Born with dark curly hair, it fell out at six months and was replaced by a light lanugo. The inheritance is evidently recessive.

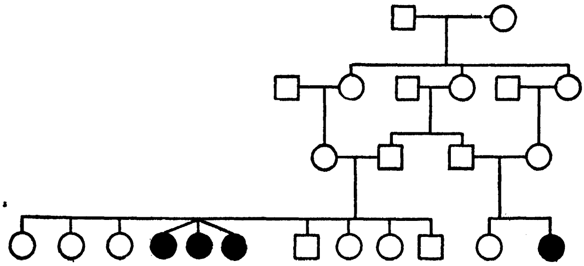

Fig. 124. Pedigree of recessive congenital hypotrichosis. (After Henckel)

The hairless condition occurs in various races as independent mutations, but appears to be less frequent than albinism. Miklucho-Maclay (1881) described two completely bald and hairless Australian aboriginals in Queensland. Their nails and teeth were normal. Hill (1881) saw two hairless sisters, probably from the same family, and reported that a number of others were hairless in this tribe.

Hypotrichosis et dystrophia unguicum or dystrophy of the nails and hair, also known as *onychogryposis*, is an ectodermal dystrophy or developmental defect of hydrotic type in which the nails are conspicuously affected, but the sweat glands are present. Oliver (1925) gives a brief account of its occurrence in grandmother, daughter and granddaughter. Most of the families have been recorded in France and in French Canada, where it is particularly prevalent; but there is one Danish family and one German (Bloch, 1925). The latter had sixteen cases in five generations, beginning with a woman having congenital lack of eyelashes, eyebrows, finger- and toe-nails. The hair and teeth were normal. The condition was dominant, as in all other pedigrees of this condition.

The French-Canadian family originated in the same part of France that the other cases came from. All cases reported on the American continent are from this source, the family having come to Canada before 1759, so the transmission has doubtless taken place over more than two centuries. Jacobsen (1928) described a branch of this family in Buffalo (Fig. 125) with 22 cases (7 ♂ 15 ♀) in five generations, and Clouston (1929) has given a full account of the family. He says it never skips a generation, and estimates that there are now over six thousand affected individuals in North America. They show every degree of the defect. The dystrophy involves nails, hair, the sebaceous glands and to some extent the sweat glands. Other ectodermal tissues are involved, e.g., the teeth, the nervous system and ectodermal glands of internal secretion. The skin is also pigmented, particularly the knuckles, elbows, axillae, areolae and pubes. Superficially the affected persons fall into two groups, (1) those with defective or absent nails and hair, (2) those with defective nails only. The hair condition is congenital hypotrichosis. Unlike some other families, the affected are no smaller than their normal sibs and their intelligence is average, but many are mentally defective. The anterior pituitary may be involved, in cases with features suggesting acromegaly (tufting of the terminal phalanges in every adult male X-rayed). Experiments with mice indicate that the condition is sublethal in the homozygous state.

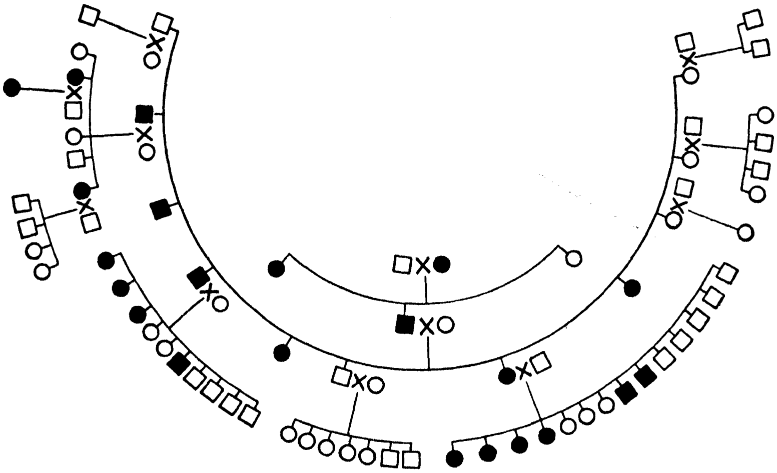

Fig. 125. Pedigree of dystrophy of hair and nails. (After Jacobsen)

Clouston saw members of five generations, two of whom are great-grandfathers. Their grandmother was the earliest case that can now be traced. She had five children with the dystrophy. One daughter was the ancestress of Jacobsen's family and a son is ancestor of Clouston's family. There are 118 affected descendants in six generations (57 ♂ 61 ♀) of this line. The sibships number 79 affected: 86 normal, the inheritance being strictly dominant with no skips. Clouston is unduly optimistic in supposing that improvements in the conditions will eliminate the dystrophy in a few generations. The laws of heredity are inexorable and even in optimum conditions the germinal defect may be expected to be handed on in its full strength. It can only be eliminated if those who are afflicted develop a restraint which they have failed to show in the past, and refrain from having descendants.

Joachim (1936) recorded another French-Canadian family with 20 cases (4♂ 16♀) in six generations. There was complete alopecia of the scalp, with absence of axillary and pubic hair as well as nail dystrophy. Eyebrows were practically absent and eyelashes sparse. The sibships numbered 19 affected : 23 normal, but there was a striking excess of affected females. Barrett (1919) reported a large family having defective hair and nails associated with *hypo-thyroidism* producing neurological disorders, feeblemindedness and abnormalities in behavior. There may be two independent genes involved. Tobias (1925) and Thompson (1928) reported dominant pedigrees of dystrophy of the nails alone.

Another family of French-Canadian extraction having nail dystrophy and alopecia is recorded by Wilkey and Stevenson (1945). There were 64 cases (37♂ 27♀) in six generations. The nail defects were in three related forms, and at least 39 of these cases had some degree of alopecia. The skin of the hands was rough and thick, but the teeth were not affected.

In the 11 published pedigrees, Cockayne found in sibships 242 affected: 253 normal; those affected were 121 ♂ : 134 ♀. In all the French families there are many blonds among the affected, although French Canadians are generally dark. There may therefore be partial linkage between blondness and the defect, as there is between dark coloring and monilethrix. As the same applied to alopecia areata, it is possible that all these genes affecting the skin and its appendages are located in the same chromosome, which also contains the locus for dark or blond hair. These would form a group of five linked genes, but some of them may be allelic to each other. The alternative is mere chance association.

The *Cagots* is the name applied for centuries to certain families who live in southeastern France, near the Pyrenees, and have some French-Canadian descendants. They probably represent the same dominant mutation as the above families. The hair becomes sparse long after birth and is of pale, almost yellowish color (hence perhaps linked again to the pigmentation locus) and they have the same onychogryposis and sparse hair on the trunk. Magitot (1892) described them. The term *cagot* is Celto-Breton, meaning descendants of lepers. In one family the sibships gave 14 affected : 11 normal. The alopecia varies, and in addition to thickened finger- and toe-nails some show absence of the lateral incisors in both jaws. The Cagots are stated to have been widespread in the Pyrenees regions in the tenth and eleventh centuries.

They were ostracized and there was a special "porte des Cagots" in the churches. According to historians they were descended from lepers. In southern France they were called Capots, in Spain Agotes.

The Nails

Certain conditions involving the finger- and toe-nails are referred to in Chap. XI as well as in this chapter. Other dystrophies involving the nails more specifically may be referred to here.

Pachyonychia congenita is a condition in which the nails become so thick and hard that a hammer and chisel is required to trim them. It may be combined with hyperkeratosis and hyperidrosis of the palms and soles, and in some with dyskeratosis of the cornea. In the original case of Jadasson and Lewandowski (1906) other symptoms in a brother and sister were keratosis of palms and soles and white patches on the tongue. Franklin (1938) described a similar case in a boy of seventeen. Cockayne (1933) listed 13 families with 14 affected : 25 normal sibs, 16♂ : 3♀ cases, showing a preponderance of males. Possibly two autosomal genes may be required to produce the condition, or an inhibitor may be present. These claw-like nails have been found mainly in Slavs and in Jews of Slavonic origin. In the Filipino family of Clemente (1928), however, it is dominant (Fig. 126). Case III. 7 was apparently a mutation, as all his relatives were normal for at least two generations. Figure 127 shows the condition of the nails in one of the children (IV. 5). The toe-nails were equally affected, the nails becoming cylindrical at the tip. They were allowed to grow long like claws because cutting them was a painful process.

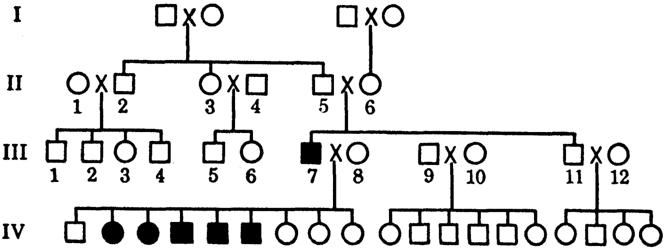

Fig. 126. Pedigree of claw fingers (pachyonychia congenita). (After Clemente)

Hyperkeratosis of the nails is a less extreme condition in which the nails become brittle and much thickened, especially at the distal end. It is strictly dominant and is found in Europeans, Filipinos, Singhalese and Tamils. A. G. Wilson (1905) described a family with seven cases in three generations. The hair and skin were normal. Exactly the same rare dominant condition was described by Murray (1921) in another family. In this pedigree of seven cases there were two or more erupted incisors at birth, which soon decayed. The nails frequently had paronychia (whitlow). Thompson's (1928) family in Seattle showed 15 cases (10♂ 5♀) in four generations, dominant with two skips. Cockayne lists 7 pedigrees with 48 affected : 47 normal sibs, 34♂ : 24♀ affected. Hobbs (1935) records a family in St. John with nail dystrophy of hands and feet, varying on one hand from a slight effect to complete absence of nail. X rays show that the distal phalanges have spatulate tips. The condition is dominant, with 11 cases (4♂ 7♀) in four generations, a strict dominant. In generation III, only one of seven affected married, whereas five out of ten of their normal sibs married, thus showing a marked effect of sexual selection. Stauffer and Simmons (1942) describe a family with hyperkeratosis of the big toe-nails only. A member married into another family with dominantly inherited sebaceous cysts. Three generations of offspring show thirteen persons with one or both defects, but no indication of linkage.

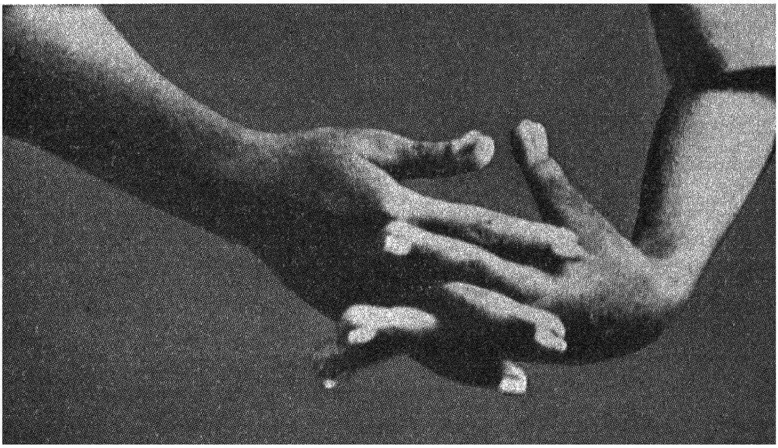

Fig. 127. Hands showing clawfingers. (After Clemente) (From the *J. of Heredity*)

Onychogryposis implies that the nails are hooked or incurved, but the name has been applied to conditions of hyperkeratosis. Orel (1928) described a family with all the nails thickest in the middle, the change frequently confined to the big toes. In some cases the nails grew out in a spiral. There were 19 cases (12♂ 7♀) in four generations, strictly dominant. He thinks the first case was a mutation. Bloch recorded onychogryposis of the *index fingers only* in a father, son and two daughters; and Köhler (1909) a family with only the toe-nails affected in four females in four generations.

In *Koilonychia* the nails are thin and flat, becoming spoon-shaped, or they may be depressed from birth. Several incomplete pedigrees show dominant inheritance. In one family only the finger-nails were affected. Cipollaro (1930) described two generations of a family with spoon nails. It can apparently arise from iron deficiency (sideropenia). *Periodic shedding of nails* was described in a French family. A man, his mother and two of her brothers were affected, several other members having defective nails. *Onycholysis*, partial separation of the nail from its bed, is hereditary, probably dominant. Wilkes (*J. Am. Med. Assn.* 122:1216, 1943) cites a case in mother and child. Fox (1940) reported 30 cases (2 ♂ 28 ♀) associated with thyroid deficiency and low basal metabolism.

Keratolysis or shedding of the whole skin is a more remarkable phenomenon. Three single cases have been described, all in men. Frank and Sandford (1891) described a unique case in which the shedding took place on the same day every year for thirty-three years. It was preceded by a feeling of malaise with fever and vomiting. The skin of hands and feet came off complete, like gloves and moccasins. Stone (1900) described a man of fifty who had six normal brothers and sisters. His skin was shed every summer, including the hair of the head, the eyebrows and moustache a few hairs at a time, so that baldness did not result. The nails were also shed. The condition is described in Gould and Pyle's *Anomalies and Curiosities of Medicine*. Although no familial case has been reported, the condition probably has a genetic basis.

Leuconychia totalis is a very rare condition in which the finger- and toe-nails have congenitally a bluish-white color. In one family, father, son and daughter and a grandson were affected; in another (Oppenheim, 1937), father and son had finger- and toe-nails bluish white, the lunula darker. Bauer (1919) cited a family with 19 cases (10 ♂ 9 ♀) in four generations, strictly dominant. All but two of them had epidermoid cysts as well. This is probably a case of linkage. *Leuconychia striata* differs in having transverse white bands on the nails (father and son). In *Leuconychia partialis* there is a longitudinal white stripe down the centre on the finger-nails only. A brother and sister with normal parents may indicate recessive inheritance. *Naevus striatus symmetricus unguis* is the name given by Oliver and Bluefarb (1944) to the condition in a girl of twelve in which the nails of both thumbs and both little fingers were affected by naevus (malformation) of the nail plates. The mother, in her pregnancy, had been treated for eruption of the palms.

Granulosis rubra nasi is a condition of sweating and redness of the skin over the nasal cartilages. It appears in young children and generally disappears at puberty, but traces persist. It is probably an irregular dominant. Cockayne (1933) collected 37 ♂ and 22 ♀ cases published in ten years, of English, French, German, Italian and Japanese families. Hellier (1937) found it in a mother and daughter, five other children being normal.

Angiokeratoma begins with chilblains, then tiny telangiectases appear which form aggregates with a horny epidermis. Pringle (1913) described a family of two affected sisters with dark hair and three normal sisters with light hair. The parents were normal. In an Italian family with normal parents, seven out of eight sibs were affected, and in a French family a brother and sister. Pringle also saw the condition in a father and his three sons, and it appeared in mother and daughter of a French family. There is also a Japanese case. If a single method of inheritance is involved it is probably one of susceptibility.

Darwin, in *The Expression of the Emotions* (p. 312), cites a number of cases of inheritance of a *tendency to blush*, and one in which mother and daughter blushed in the same peculiar manner. Excessive blushing has a psychological basis, while the blush area has a physical basis. Hutchinson (1891) cites a case of three brothers and a sister (whose normal parents were first cousins) having a flush-patch on the cheek, followed by permanent redness of the skin, perhaps due to some vasomotor abnormality, but ending in a condition between lupus erythematosus and acne rosacea.

An inherited anomaly of the hair is called *catatrichy* or natural bangs. A front lock of hair about 3 in. wide grows to a length of 5 or 6 in., then the hairs fall and are replaced by new ones. Stoddard (1939) described a family in which it was dominant, with 9 cases (1 ♂ 8 ♀) in four generations. It is not seen in men because their hair is cut short, but was observed in a boy.

Anidrotic ectodermal dysplasia, without sweat glands, is much rarer than the hydrotic type, but is a well-known syndrome in which the individual is toothless or deficient in teeth, frequently with conical or peg-shaped incisors; fine, pale, scanty hair; chronic rhinitis; absence of sweat glands and, in some cases, of lachrymal glands. Affected persons are short and slight, of delicate constitution, the bridge of the nose is depressed, the jaws and frontal sinuses undeveloped and the lips thick from a compensatory development of the orbicularis oris muscle (Fig. 128). The skin is smooth and dry and the individual suffers much from hot weather, although showing no discomfort in cool weather. In hot climates they acquire the habit of lying in water or having cold water thrown over them. Dogs, pigs and cattle lack functional sweat glands. Although the teeth and sweat glands are both ectodermal structures, it is not clear why they are so specifically affected by one gene.

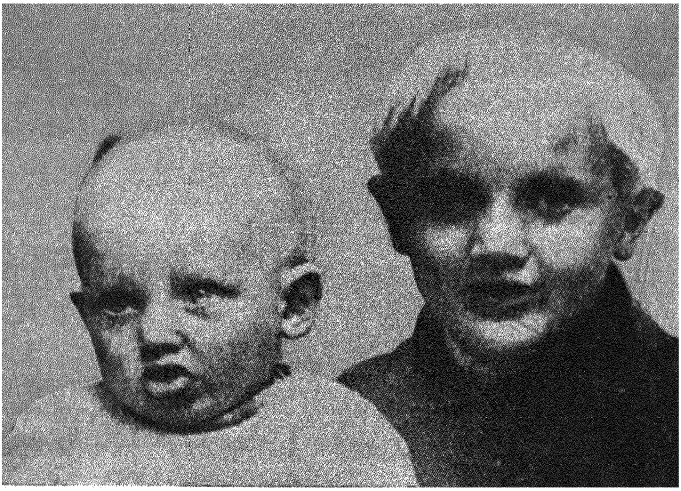

Fig. 126. Anhidrotic ectodermal dysplasia in brothers. (After J. Smith)

Thurnam (1848) described the two earliest cases, in a man and his male cousin. Almost complete absence of hair was combined with presence of not more than four teeth and absence of sweat and tear glands. A post-mortem showed the skull to be thick and of almost ivory-like density, the vermiform appendix double the normal length. Their grandmother had extremely delicate skin with very little perspiration. She was probably a carrier. Thurnam referred to two Jewish brothers reported by Danz in 1792. The next recorded case (Guilford, 1883) was a man of forty-eight with all the symptoms as well as almost total absence of sebaceous glands. Two of his eight children lacked many teeth. MacKee and Andrews (1924) described eight cases in a family with typical symptoms. Gordon and Jamieson (1931) record a typical case in a female of seventeen, born of Russian Jewish parents. They found twenty-one previous cases in the world literature. Černy (1924) recorded the case of a girl of twelve whose ancestors and sibs were normal, so she may have been a mutation. Besides soft, thin hair and anidrosis she had no teeth in the lower jaw.

Many families are now known in which the condition is a sex-linked recessive, and others in which it is a straight dominant. Thadani (1921, 1934) gave a short account of a Hindu Amil community in Hyderabad in which the males were toothless (Bhudas), bald and extremely sensitive to heat. They are descended from one ancestor and are now in the sixth generation. In the third generation there was an affected man and his normal (carrier) sister. In the fourth generation there were eight affected families, and twenty in the fifth, still more in the sixth. In the fifth generation one woman was "partially abnormal" and she produced an abnormal daughter. Toothless men have only normal children; the sons have only normal descendants while the daughters have normal daughters (half of them carriers) and half the sons are toothless. A fifth-generation abnormal male also produced an abnormal daughter. The condition is inherited exactly like color-blindness and the two affected females are apparently due to variable dominance. This is no doubt the family referred to by Darwin (*Animals and Plants*, 2nd ed.). Hutt (1935) points out that W. Wedderburn's observations of the family were probably between 1868 and 1875. He recorded ten men affected in four generations. Thadani reports eight "families" in the fourth generation, whereas there were only six females in the third generation who might transmit the condition. If we read "eight affected males" in the fourth generation, these with the case in the third generation and the original mutation would make up Mr. Wedderburn's ten. The latter's observations show that occasional molars and small incisors are present. Counting twenty years to a generation, the original mutation would have appeared about 1780.

Roberts (1929) described a family in Illinois with the same condition, ten cases (males) in five generations. Three of the carrier females had patches of smooth skin without sweat glands on their body. The enlarged finger-prints of the males show the absence of openings of the sweat ducts. Rushton (1934) described an English family with 6 cases (5 ♂ 1 ♀) in two generations. They were all descended from three (carrier) sisters. Affected males were small and delicate, with no sweat and often no lachrymal glands; some teeth missing, others conical; fine, fair hair and chronic rhinitis leading to loss of smell. Schwartz (1935) described four brothers in a Texas family, who in summer spent the greater part of the day immersed in water. Three of them died of influenza. The mother and one of her sisters lacked the upper permanent canine teeth, and the sister had dry hair. Their nine sibs were normal. The condition was thus incompletely recessive in the females. The boys had sparse, dry hair, no eyebrows, prominent supraorbital ridges. The nails were normal, as well as the reflexes and mentality. A boy in a family of German descent, whose parents, brother and sister were normal, developed a high fever when ten days old. At five years he spent the summer mostly in a tub of water. The teeth all erupted but became carious, the hair sparse, extremely fine and dry. There was no saddle nose nor prominent supraorbital ridges, the lips were normal but the mucous membrane was reddened, the finger- and toe-nails concave with broken tips.

A father and two children with a mild form of anidrotic ectodermal defect were described by Brain (1937). Fleischmann (1935) made a general study of the condition. He found thirty single cases recorded and he also collected seventeen pedigrees. Three show lack of teeth and hair, and three premature alopecia transmitted by normal females. In four pedigrees of *ozaena* (foul nasal odor from chronic rhinitis) and four showing *lack of teeth* the inheritance differs in that normal females do not transmit. He concluded that anidrotic hypotrichosis is due to several genes, some sex-linked, others not. This hypothesis seems unnecessarily complicated. The results can be explained by one recessive gene in the X-chromosome, with variable expression and occasionally dominant in the $\underline{X}X$ female. Goeckermann (1920) reported a unique case of a female lacking sweat glands and sebaceous glands, with hypotrichosis and dental aplasia.

It is well known that the mammary glands are modified sweat glands, so it is not surprising that absence of sweat glands is sometimes accompanied by absence of nipples in the male. This may have occurred in some families without being recorded. Hutchinson (1886) reported the case of a boy of three and a half years with a peculiar withered and pinched look, fingers shrivelled, finger- and toe-nails concave, head large, anterior fontanelle not quite closed, scalp bald except for a quantity of down, skin very thin, atrophic, with no nipples, but very intelligent. The mother was bald from six years of age (alopecia areata). Her five daughters were normal. Tendlau (1902) reported a similar case in a man of forty-eight years in a sound family. He had no nipples, very little hair, no teeth in the lower jaw, two incisors and two molars in the upper jaw. The incisors fell out at twenty. His skull was of peculiar shape, he could not sweat and his nails were concave. All his relatives were normal. Glass and Yost (1939) record a family in the northwestern United States with a somewhat different expression of this remarkable syndrome (Fig. 129). Case I. 2 was eighty-three years of age, never sweat, was subject to severe headaches, had no mammary glands, quite thick lips and stomach trouble. One daughter showed the same condition, and one grandson, except that it is not stated whether he lacked nipples. All three have brown hair. It seems likely that in this family the condition is an irregularly dominant sex-linked character, but the children of the normal women are not mentioned.

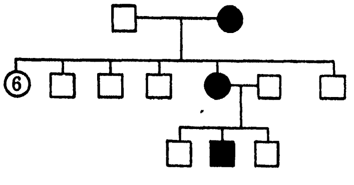

Fig. 129. Pedigree of ectodermal dysplasia. (After Glass and Yost)

Smith (1931) described two brothers (Fig. 128) with sparse, fair hair, thick everted lips, depressed nasal bridge, large projecting ears, no sweating, upper incisors conical and no other teeth except two molars on each side in each jaw. Zeligs (1932) described a similar Jewish boy of ten months, who was feverish in hot weather. He lacked sebaceous and sweat glands, but a skin section from the abdomen showed sweat glands. The hair follicles were normal but hair sparse. The nails were normal, but teeth were absent except two peg-shaped upper central incisors. Weech (1929) described two Jewish boys (brothers) in the same condition and considered the earlier literature. In addition to a dry, glossy skin, they had papular lesions on the face, a small sella turcica and defective mucous membrane of the nose, mouth and pharynx, as well as defective hair, teeth and sweat glands and heat intolerance. He also described a girl of seven years with two normal sibs. Her father's family showed scarcity of hair and its early loss, he and two of his uncles also lacking certain teeth. The girl at birth had no hair on head or eyebrows, the nails were small and concave, the growth of hair exceedingly slow and sparse. Nine teeth erupted in the first twelve months, but none since. She had no lower incisors and the upper ones were pegs. She perspired freely, but had prominent thick lips, the bridge of the nose deeply concave. This accumulation or exaggeration of effects partly adumbrated in the father's family is a not unusual situation and may have a bearing on the origin of some mutations. A case of similar character was described in Stockholm (Ihre, 1932). A boy of six and a half had no teeth or dental primordia. The parents were normal and unrelated. The boy's skin was dry and without perspiration, his hair sparse, fine, lanugo-like, light brown. Eyebrows were nearly lacking, eyelashes thin and irregular. The thumbs were abnormally short. His mother's family all had remarkably small thumbs, and a maternal aunt had four persisting milk teeth. Knorre (1936) has a pedigree of mother, daughter and grandson affected with *ozaena*, combined in varying degrees with hypotrichosis, anidrosis and anodontia.

The recessive sex-linked form of anidrotic ectodermal dysplasia has been described in Anglo-Saxons, Swedes, Germans, French, Russians, Jews, Hindus and Singhalese, but does not appear to occur in Mediterraneans, Negroes or Mongolians.[8] The dominant form, which is indistinguishable, has been observed in a number of Anglo-Saxon families, but may be incompletely developed, as in the girl above, who had sweat glands. Cockayne (1933) has listed a number of further pedigrees of both types. Levit (1936) believes that both types are the same, representing a conditional dominant with sex-linkage, as there is no case of an affected male having an affected son. De Silva (1939) described a Singhalese family with two affected males, sex-linked.

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[8] Coello (1943), however, describes the case of a Chinese man in Cuba who had little hair, lacked sweat glands and several teeth and was mentally deficient.

Clouston (1939) reports four male cases in Canada, two of them brothers, so the inheritance is presumably recessive sex-linked. The mucous glands of the nose and throat are shown to be few or absent, thus producing the rhinitis, and the condition is probably a cause of death in infancy.

Sunderman (1941) studied three brothers in an Italian family with normal parents and seven normal sibs. This case was probably recessive sex-linked. At a high temperature they panted like dogs but did not perspire, and two of them could not shed tears. The noses were saddle-shape, the lips thick and negroid; two had rhinitis and could not smell. Felsher (1944) records another sex-linked pedigree with five affected males, and shows that the condition is *hypohydrotic* rather than anhidrotic. In the case studied, the eccrine glands were 5 to 7 per cent of normal on the extremities and practically absent from the abdomen and face. The apocrine glands were abundant in the axillae and on the chest.

Racial differences in the distribution of sweat glands have been shown by Glaser (1934). He found that in the Bantu they are more numerous per square centimeter in most parts of the body than in Europeans. This is doubtless an adaptation to a hot climate.

Beadle (1926) gives a pedigree in three generations showing *absence of certain teeth.* They were also irregular in time of eruption both of the deciduous and the permanent teeth, and in the number of teeth missing. The lacking teeth included both incisors and molars, but not canines. The condition was a simple dominant, five normal and five abnormal occurring in a family of ten. Those with tooth deficiency were dark-haired in fifteen cases and light-haired in three. The ratio of normals was *ca.* 14 light: 1 dark, indicating linkage with crossing-over between the genes for tooth anomaly and dark hair. Crosman (1927) cited from Guilford (1883) a case of an edentulous woman also without hair. Her son was in the same condition, and six of his children were normal, two having undeveloped teeth. His normal sister had eighteen children, one of whom was without teeth or hair.

Jones (1933) described a Jewish family in Ontario with *multiple cysts of the jaws.* Two boys and a girl, aged six, five and four years, had cherubic cheeks and enlarged jaws, with many teeth missing, but with jaws enlarged by cyst formation and the submaxillary lymphatics enlarged. There was nothing similar in any of the relatives, and there were indications that the growth might be self-limiting. It probably has a recessive genetic basis.

Defects of the Teeth

A search of the dental journals would no doubt disclose many cases of inherited tooth defects. It has only been possible to collect a few of these, but various other pedigrees of dental defect will be considered. McQuillan (1870) described a case in which father, son and grandson lacked an upper lateral incisor. A second son had very dwarfed incisors and part of his children were the same. In mother and daughter of another family the upper lateral incisors were within the dental arch, making the canines prominent. Lucas (1888) noted absence of an upper lateral incisor in father and daughter. From other cases of missing or peg-shaped incisors he concluded (1904) that this condition is closely related to harelip and cleft palate. Wheelon (1925) states that the *upper lateral incisors* are most commonly absent or peg-shaped, and these are regarded as the least useful in the dental arch. In three years he collected twenty cases, and his pedigrees indicate that the character is dominant. In II there were 9 cases (2♂ 7♀) in four generations of a missing right (left in one girl) upper lateral incisor (no skip). In III, 9 cases (3♂ 6♀) in three generations of a missing right (left in one) upper lateral incisor. Kaplan suggested some connection between gonad deficiency and lack of the upper lateral incisors, but Wheelon cites a case of a female intersex with a perfect arch of teeth.

Baisch (1931) cites a girl with absence of lateral incisors and delayed cutting of central incisors, together with polydactyly, syndactyly, almost complete anonychia of fingers and toes and hypoplasia of the distal interphalangeal joints. Her family in four generations showed three cases of syndactyly and one of bilateral clubfoot.

Schultz (1932), in an important contribution, states that in man the medial incisors are larger than the lateral ones in the upper jaw, but smaller than the laterals in the lower jaw. The results of many writers show an evolutionary trend to reduce the human dentition in connection with a shortening of the jaws. The reduction affects both ends of the series, the third molars (wisdom teeth) and the incisors. It is the smaller incisors, i.e., the upper lateral and the lower medial, which are most likely to be reduced to pegs or missing. Röse, in series of cases totalling 15,000, found degeneration or absence of the upper lateral incisors in Scandinavia 6 per cent, Central Europe, 2 to 4 per cent, Greeks, 1.4 per cent, colored races *ca.* 1 per cent. Lack of these incisors is, as the pedigrees show, more frequent in females than males and much more frequent in the permanent than in the deciduous dentition. Hrdlička obtained similar results, finding in one thousand white Americans degeneration of the upper lateral incisors in 3 per cent, congenital absence of one or both lateral incisors in 1.4 per cent of males and 3.0 per cent of females.

That the Primates show the same evolutionary tendency is indicated by the fact that Schultz found a case of extreme reduction in the upper lateral incisors of a gorilla, and a howler monkey with only three lower incisors. All of which goes to show that an evolutionary tendency of this kind is a slowly moving concern of the germplasm.

In a human family, Schultz (1934) found in four generations seven cases of absence of the upper lateral incisors and three cases in which they are vestigial (in one case on one side only). The affected are female in all ten cases, the numerous males in the pedigree being normal, nor do they transmit the condition. This hologynic inheritance indicates end-to-end union of the two X-chromosomes. If the condition was merely sex-limited, then males should transmit; but we have already observed from other pedigrees and statistics that the condition is uniformly more frequent in the female, so perhaps this may be only an extreme case of a dominant character which is more frequent in the female.

Small or absent upper lateral incisors is perhaps the most common dental anomaly. A number of dominant European pedigrees have been published, and the condition was found in the skull of a Senegalese Negro. The homozygous condition of this gene is unknown. Sergi (1914) reported 8 cases (6 ♂ 2 ♀) in three generations of a Piedmontese family in which the upper lateral right incisor was missing and the left very small, and cites other families with the same dominant inheritance. Thomas (1926) cites a family with eight cases of these incisors being small or missing, but the dominance is irregular. Cockayne found the sexes equally affected, 33 ♂ : 39 ♀. Ashley-Montagu (1940) regards the variability of the upper lateral incisors as reflecting a tendency which is as old as the common ancestors of the Hominidae and the Anthropoideae and is expressed in different degrees in different races. The Chinese show *ca.* 2 per cent, Japanese, 4 per cent of missing or reduced lateral incisors, pure Negroes, 1.5 per cent, mixed, 5 per cent. Such relatively unmixed races as the Australian aborigines, Bantu and Melanesians very rarely show it.

Keeler (1935) collected many pedigrees of tooth defects from the dental literature. He concluded that dentists had overemphasized syphilis, diet and endocrines as causes of dental irregularities, although such conditions often produce anomalies similar to those which are hereditary. He cites several pedigrees of missing upper lateral incisors and describes a family in which five females in three generations lost the upper right lateral incisor by decay at ten to thirteen years. In another family two brothers and a sister failed to shed a deciduous upper right molar. The teeth appear to be as individually under genic control as the bones. Keeler cites the three families of Moody and Montgomery in which there was *fusion of the lower incisors* in the females only: I. Twelve cases in three generations. II. Five cases in two generations. III. Four cases in three generations. The sibships numbered 20 affected: 17 normal; hence the condition may be an autosomal dominant although no males were affected. There was no skip. The inheritance appears to be hologynic.

Keeler and Short (1934) described a family (Fig. 130) in which absent or peg-shaped upper lateral incisors were inherited as an irregular dominant in one family. A frenum or space between the central upper incisors (*gat-toothed*) and lack of upper lateral incisors was inherited in another family. Intermarriage produced a child (III. 5) who lacked the upper lateral incisors and a lower bicuspid on each side, having also a peg-shaped lower left central incisor as well as the gat. She was probably homozygous for the gene causing absence of upper lateral incisors. Yamagouchi (in Keeler, 1935) found a trema or gat between both upper and lower median incisors in a father and two sons (dominant).

Adams (1932) has a pedigree of a family with *no incisors.* There were thirteen cases in three generations, with three skips which may be ascribed to low penetrance of the genes or the presence of a common inhibiting factor. In one case there was also an impacted right upper canine. In a pair of female twins, probably identical, the upper incisors were missing in one and the lower in the other. Michelson's (1885) family (Fig. 121, p. 339) had missing upper incisors with hypertrichosis on the chest, shoulders and back, and in some cases on hands, nose and ears. Evidently these genes were not linked.

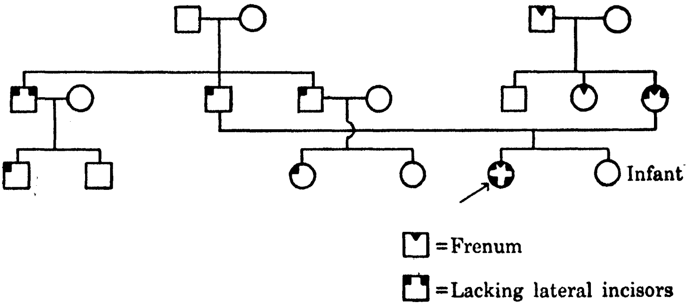

Fig. 130. Pedigree of missing upper lateral incisors and a median frenum. (After Keeler and Short)

Campbell (1934) reported teeth lacking in 35 out of 2000 patients. Combining his records with those from the literature, he found both upper lateral incisors missing in 97 out of 3550 cases, or 2. 7 per cent. This probably gives a reasonable estimate of the gene frequency.

Grüneberg (1936) described two German Jewish families, in one of which there was (1) lack of permanent upper canines, as shown by X rays, and (2) lack of wisdom teeth. The milk canines were often persistent. Lack of canines was dominant, with seven cases in three generations. Lack of wisdom teeth in the mother and four of her five children also suggests dominance. Three of these children also lack the upper canines.

As regards the *loss of third molars*, the Eskimos appear to be less advanced than Europeans. These teeth are lacking, generally on both sides, in 16.6 per cent of adult Eskimos, and more frequently in females than males. Retardation, reduction and suppression are stages in the loss of the third molar. Schultz (1926) cites ninety-seven Negro skulls with third molars in every one of them, so the Negro is least advanced in this respect. By comparison, in 250 Dutch skulls the third molars were absent on one or both sides of the upper jaw in 19.5 per cent, from the lower jaw in 22.6 per cent, one or more being absent from 70 per cent of the skulls. In Chinese at eleven years the teeth always number twenty-eight, in Europeans, twenty-four, the third molar appearing at fifteen to sixteen years. The deciduous molar was permanent in thirty lower jaws in the Amsterdam Museum. Yamazaki (1930) has many observations on the asymmetrical development of the mandible and the wisdom teeth. Schultz (1934) found that in a monkey, *Ateles geoffroyi*, the third molars were congenitally absent in 15.4 per cent of the specimens from East Nicaragua but in only 3.5 per cent of those from Chiriqui, Panama.

That the suppression of the upper lateral and the lower medial incisors is not merely a straightforward steam-roller tendency, is shown by the pedigree of Huskins (1930). The absence of medial incisors from both jaws in both dentitions was a sex-linked partial dominant in an English family with 7 cases (5♂ 2♀) in three generations. In one woman the single gene was completely dominant, and in another partially so, since she painfully cut the missing incisors at thirteen years of age. The other six females in the pedigree, two of whom are known to be heterozygous for the gene, nevertheless all had normal teeth. This variability in the penetrance and expressivity of a sex-linked gene in the female sex also occurs in the case of color-blindness, hemophilia and various other conditions.

In an isolated Swiss village with much inbreeding for centuries, Jöhr (1934) made an extensive study of the dental conditions, especially as regards the absence of upper lateral incisors and the presence of caries. The population is strongly brachycephalic and has fair features, — a widespread type in Switzerland according to Schlaginhaufen, who either represent a separate race or are a mixture of Nordic and Dinaric characters. In 162 persons measurements were made of the jaws, and records bearing on the constitution. About one-third of these showed reduction or absence of the upper lateral incisors, and an extensive pedigree confirms the dominant inheritance of this condition, sixty cases of the more extreme conditions being recorded among the descendants of a single couple who lived at the beginning of the eighteenth century. He regards this not as a phylogenetically progressive character, but simply as a minus mutation accompanying small jaws, in contrast to other inbred populations both Swiss and Melanesian. In a neighbouring valley the anomaly is only found in 2.4 per cent of the people. He confirms the results of other Swiss workers that hereditary (family) factors play an important part in dental caries.

Slightly more extensive is the defect in the family of Pitts (1923). Three sons of normal parents showed absence of deciduous and permanent central incisors and also of the permanent lateral incisors, the deciduous lateral incisors being peg-shaped. In another family Pitts reported mother and two daughters with absence of upper lateral incisors, unilateral in the mother, bilateral in the daughter, one of whom also lacked a lower incisor. Miller (1941) records a Japanese family in which the grandmother, mother and two children had three instead of four lower incisors. Komai (1934) published Japanese pedigrees of missing upper lateral incisors and absence of premolars. He also reports families with abnormally large upper incisors and others with conical or absent incisors (see Keeler, 1935). One Japanese family had *giant upper median incisors*, a not uncommon condition in Japan. There were 7 cases (2 ♂ 5 ♀) in three generations (dominant). In another Japanese family abnormally large median incisors were present in 6 cases (2 ♂ 4 ♀) in three generations (dominant). In another dominant pedigree in Japan, four males in three generations had many missing teeth. One lacked fifteen teeth, another nineteen. Brekhus, Oliver and Montelius (1944) found 202 persons with dental anomalies, mostly missing teeth, among 11,487 in a dental clinic. Second incisors, second premolars and third molars were most frequently lacking, and several pedigrees are given.

Johnson (1940) points out that both environment and genetic constitution have to be taken into account in the study of malocclusion. Following Stockard, he shows that growth deviations in the human face correspond closely with those in modern breeds of dogs, such as the bulldog, bloodhound, Pekinese and Boston terrier.

In two Italian families, the *absence of all incisors* was inherited as a constant dominant condition (Ovazza, 1922). Gardner (1927) records a family with 14 cases (2 ♂ 10 ♀) of many missing teeth in six generations, dominant. A girl and her father, who were examined in detail, were lacking all incisors, canines, first and second bicuspids and third molars, i.e., twelve teeth above and nine below. X ray showed that buds of these teeth were also absent. McCracken (1931) recorded the case of a boy who cut his first teeth at two years — two long, fang-like lateral incisors. At three years an upper molar erupted. X rays showed only six unerupted teeth. As the two preceding generations and the two elder brothers were all normal, this was probably a mutation.

In an experimentally treated (X-rayed?) line of white rats (Jones, 1924) an inherited tooth anomaly appeared in which the incisors grew into tusks which curved back into the mouth or over the lips. Greep (1941) records absence of incisors in the white rat. When bred the condition was found to be recessive. The gene was closely linked to curly in chromosome II. Long incisors are characteristic of the Rodentia. It is probable that the later Proboscidians lost their lower tusks by a mutation.

Villain and Villas record a family with normal parents, three of the five children lacking the upper lateral incisors, all upper premolars and the lower central incisors, as well as all the second and third upper and lower molars. Other cases of hereditary partial anodontia have been recorded by Chipps (1932). Campbell (1929) recorded a Jewish family with nine cases and seven suspected cases of missing teeth. These were mainly the upper lateral incisors, but the median lower incisors and the anterior molars may also be lacking.

In deer, the canine teeth are normally absent, but in certain species with rudimentary antlers, such as the elk, they are well developed.

In German Shepherd dogs the teeth and jaws are large, in Pomeranians they are small (see Johnson, 1940, Stockard, 1941). In the F_2 from this cross some animals have large teeth in small jaws. They describe numerous cases of malocclusion in various dog hybrids. There can be no reasonable doubt that similar (though usually less extreme) conditions in man have the same explanation, genetic hybridity.

That the teeth can be used for identification purposes is shown by Kadner (1933). Two babies were exchanged in hospital in 1919. One mother recognized that the exchange had taken place. In 1931, blood group tests gave no help. But casts of the teeth and jaws of both families showed which were father and son. It is almost impossible to compare the teeth of three generations simultaneously, but Korkhaus (1930) found that in six pairs of identical twins casts of the dentition showed many detailed correspondences. The form, size and color of the teeth, the Carabelli tubercle,[9] tooth hypoplasia, etc., agreed. The *diastema* is said to be dominant. It was found four times in absolute conformity in identical twins but only occasionally in other twins. Casts of a six-year-old pair were identical in the central upper diastema and the teeth as well as in the width and height of the palate. Weninger (1933) gives pedigrees of twenty-six families with a median diastema or trema, showing it to be a rather strict dominant.

Bachrach and Young (1927) made a statistical comparison of dental resemblances in identical and fraternal twins. MZ twins showed greater similarity as regards tooth eruption, amount of dental caries and type of dental occlusion. Ashley-Montagu (1933) cites several other cases of close similarity in the dentition of twins and describes a remarkable instance in a pair of identical male twins. When the father chastised one, the other cried in sympathy. Both showed strong cyclothymic tendencies in a six-months cycle, but D. was in the calm stage when G. was in the excited stage, and vice versa. Radiograms of the teeth at six years of age showed "almost uncanny likeness." The form and dimensions of the dental arch were extraordinarily alike, as shown by X rays, casts and measurements, as alike "as it is possible for any two things to be." "They were indistinguishable in form of the teeth, crown patterns, grooves, ridges, orientation, state of eruption and calcification." There was also in each a pathological resorption of the upper right second deciduous molar with an invasion of the resorbed area by the first permanent molar. The dentition, in short, was entirely genotypically determined.[10]

Teeth with deficient or absent roots have been recorded (see taurodont teeth). They have thick dentine and no pulp and are soon lost. In a German family, grandfather, daughter and six of seven grandchildren were affected. Another case with dominant inheritance is in *Eugenical News* 13:104. The inheritance of the *fifth tubercle* in the last two human molars requires investigation, as does also the occurrence, size and structure of third molars. That Bolk's paramolar tubercle or cusp is genetically determined is clear from Dahlberg (1945), who records the cusp bilaterally present on the lower first permanent molars in a white woman and in two Melanesian mandibles. In one of the latter all six molars had the extra cusp on the buccal surface.

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[9] This is a diminutive cusp on the lingual surface of the mesial lingual cusp of the maxillary first molar. Dietz (1944) found the Carabelli cusp, in one of its forms, in 72.3 per cent of 1000 cases studied. Gregory (1920, p. 152) states that this structure (also known as *tuberculum anomalum*) is derived from the cingulum and is found on the first and second molars. It occurs in Neanderthal man and is very rare or absent in anthropoids, but one case was found in a gibbon. It is frequent (p. 174) in many modern races and Gregory regards it as a primitive human character, of high frequency in the second milk molar.

[10] It is rather extraordinary that some writers who recognize this extreme detail in physical heredity nevertheless affect to deny any inherited psychological differences at all between human racial types.

✓*Defective or absent tooth enamel* is another rare condition which may affect both sets, but without effect on nails, hair or skin. These teeth are often brown, but they do not ache. Sinha (1918) described a Hindu family in Bengal with brown teeth, 8 cases (4 ♂ 4 ♀) in three generations, dominant. Bampton (1914) described two families with dark brown teeth, dominant sex-linked in one, with 14 cases (2 ♂ 12 ♀) in five generations. They enjoyed good health and lived to old age. In Moore's family (1924) the condition was strictly dominant, with 16 cases (13 ♂ 2 ♀) in five generations. Pflüger's (1929) family had twelve cases with defective enamel in four generations. The crowns of the teeth were worn down in early youth. Cockayne (1933) cites nine families totalling 86 affected : 51 normal in sibships. The sex-ratio of affected was 47 ♂ : 48 ♀, but the excess of affected is unaccounted for. Clark and Clark (1933) described two families, which are believed to be related since they use the same name for the enamel defect. An ancestor bearing this defect is believed to have been a passenger in the *Mayflower*. In a man of twenty the teeth are worn down to the gums. The condition is strictly dominant, with a total of 39 cases (19 ♂ 20 ♀) in six generations, the sibships numbering 37 affected : 24 normal. In Macklin's (1938) family, with seven cases in three generations, both sets of teeth showed the same defect; they were translucent, very soft, worn down and carious. The enamel cells (ameloblasts) appear to be absent. Haldane (1937) pointed out that in one of Bampton's families the defective enamel was inherited as a dominant sex-linked character. An affected father transmitted the condition to his eight daughters but to none of his four sons. A less likely alternative is that of incomplete sex-linkage, with crossing-over between homologous parts of the X and Y. Keeler (1935) cited four families with teeth lacking white enamel. There was a total of 77 cases (39 ♂ 38 ♀) in four to six generations. In these families, lack of enamel is clearly a simple dominant.

Hodge and Finn (1938) give family histories of *opalescent dentine* with extreme translucency, discoloration and friability of the teeth. Guilford in 1887 recorded the case of a man of twenty-six with the crowns of his teeth worn down to the gums, the condition present in three generations. Hodge and Finn record three new families in which opalescent dentine is inherited apparently as a simple dominant: (1) a family of Italian descent with eleven cases in four generations, (2) a German-Irish family with seven cases in four generations, (3) an American family with eight cases in four generations. The dentine is soft and easily worn, yellow or deep brown in color. The tubules show great variation in direction and may be absent, the pulp chambers being more or less obliterated. The chemical composition of the dentine is more like that of compact bone, the tubules resembling the osteodentine of sharks' teeth. The X-ray diffraction pattern shows that the inorganic portion of the dentine is hydroxylapatite, as in normal enamel and bone. The dominant gene for defective enamel, which is by no means rare, appears then to be generally autosomal, but in the X-chromosome in one family. See Hodge *et al.* (1940) for histological and chemical studies.

Finn (1938) analyzed the recorded cases of opalescent dentine. He found 220 matings, which produced 383 opalescent (200♂ : 183♀) : 357 normal, showing the presence of a single dominant gene. Roberts and Schour (1939) described a family in Illinois with opalescent dentine, 23 cases (11♂ 12♀) in six generations, strictly dominant, the sibships numbering 22 affected : 25 normal. In another family there were six cases in four generations.

In six families enamel defect is associated with lamellar cataract and fits. The inheritance is dominant, but it is not clear whether this is a syndrome or a case of linked genes. The same applies to Nettleship's family with juvenile cataract and defective enamel.

Korkhaus (1931) made a study of tooth-color in twins, using the dentist's tooth-color ring, which contains thirty slightly different tooth shades for matching purposes. His results show that *tooth shade* is almost entirely genotypic in determination. In 51 MZ pairs only 3 showed slight difference. It has no relation to the general pigmentation of the body, and there is no correlation between tooth color and eye color.

Cases of *microdontia*, in which all the teeth are very small, have often been recorded. The pedigrees are very inadequate, but the condition may be recessive. Babies born with *erupted teeth* were known to the Greeks and Romans. A baby may be born with one to four erupted incisors, which soon fall out. There is generally no associated defect, but in Murray's family (Cockayne) there were hypertrophied nails in seven members and erupted teeth in six of them. This is probably a case of linkage, or perhaps pleiotropism. Erupted teeth have been recorded in (1) mother and daughter, (2) brother and sister and the latter's son, (3) three sisters, (4) two sibs, (5) mother and two children, (6) a girl and her aunt. The condition is probably an irregular dominant, but the irregularity might be due to the presence of an inhibitor or to two genes being required.

Supernumerary teeth are often recorded in relatives, e.g., a supernumerary palatal to the incisors in (1) mother, daughter and son, (2) two sisters.

Rutherford (1931) recorded a family with *hypertrophy of the gums*, dental defect and congenital corneal opacity (Fig. 131). Case II. 2 had only two lower central incisors, which were peg-shaped. She had hypertrophy of the gums so that the mouth could not close. This was removed at nineteen and her teeth only erupted at fifteen to nineteen. The condition is probably dominant. Case IV. 1 had six teeth when eight months old. Hypertrophy of the gums alone has only been reported in single cases and is probably recessive. Goblirsch (1930) found in a study of 2112 patients that third molars (wisdom teeth) were less frequent in men than women. One or more were missing in 20.9 per cent of individuals, and all four were undeveloped in 2.33 per cent.

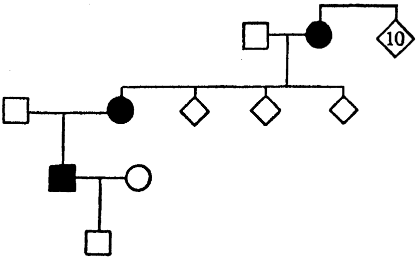


Fig. 131. Pedigree of hypertrophy of the gums, dental defect and corneal opacity. (After Rutherford)

Early dental decay was reported in a striking pedigree of Sedgwick (1863) with eleven cases (all female) in three generations (Fig. 132). This type of hologynic inheritance would be explained if the two X-chromosomes in the females were attached. Many causes of dental caries have been suggested and it appears clearly to be related to diet. Many primitive or isolated peoples, such as the Eskimos and the inhabitants of Tristan da Cunha, have perfect arches of teeth, but natives in many parts of the world have been shown to develop defective teeth after adopting the foods of civilized man. Probably in both the cases mentioned heredity plays a part, i.e., the families have teeth that are resistant to caries. On the other hand, there is evidence that prehistoric man sometimes suffered from toothache, and Schultz found dental caries to be common in wild monkeys. Lack of vitamins may be a contributing cause in modern food. Bunting (1933) concludes that dental caries is a bacterial disease of the oral cavity, related to certain constitutional states and inherited characters as well as to

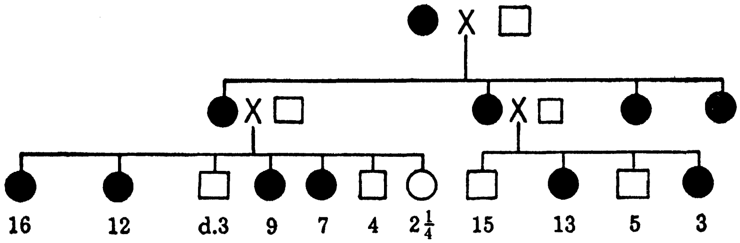


Fig. 132. Hologynic inheritance of early decay of teeth. (After Sedgwick)

age and bodily health. He states that 5 to 10 per cent of people are immune to *Bacillus acidophilus* and so protected from caries. This immunity is probably inherited. Price (1923), in an extensive study of dental infections, classifies persons as non-susceptible, acquired susceptibles and inherited susceptibles, the inheritance being 23 per cent through the maternal and 21 per cent through the paternal side.

Pfanner (1930) examined one hundred families of school children near Zürich, with their parents and grandparents. Four bad teeth were accounted a carious condition. The inheritance factor is evidently not simple. The author suggests one dominant factor (**E**) for mechanical resistance to bacterial attack and another (**I**) causing immunity. In the cross **EeIi** × **EeIi** the parents would have sound teeth while the children **eeII, EEii, Eeii, eeIi** would have carious teeth.

Walker (1936) made a study of dental caries in 679 mountain peasants in three isolated Alpine valleys with about 1000 inhabitants. Although much inbred, degenerative conditions were not found, apart from caries, which was present in 91.3 per cent of the people. This is attributed to the adoption of white bread nearly a century ago. Thirty-three pedigrees of three or four generations confirm studies by Vogt, Hanhart and others that resistance to caries is based on a true hereditary factor.

Statistics show a definite geographical distribution of caries in the United States. In the Civil War, the rejection rate for dental defects was 20.5 per 1000, the men of New England having the poorest teeth. In the war of 1914–18 the mean rate was 24.2 and the conditions in different states were strikingly parallel to those of the 1860's, Arkansas being lowest with 2.9 per 1000 and Vermont highest with 102.85 (East, 1942). In all races there is a higher incidence of caries in females than males. Hunt, Hoppert and Erwin (1944) selected from a stock of rats one strain highly susceptible to caries (on a certain diet), the other highly resistant.

Cases are recorded in which *malocclusion* and irregular teeth result from crossing between races with large and small jaws and probably they can also arise from unsuitable food and malnutrition.

The dentition of the Dionne quintuplets has been carefully followed. They are monozygotic and show malocclusion. Ford and Mason (1943) give an account of their dentition from two to seven. The mandibular arch in all five children is narrower than the maxillary arch, leading to malocclusions which are traced back to infancy.

Sir Arthur Keith distinguished between *taurodont* molars in which the body of the tooth is long and the roots short, and cynodont teeth in which the roots are long and the body reduced. The former are found in cud-chewing animals such as the ox, the latter are typical of carnivora. Taurodontism is expressed in various degrees in primitive human races. Shaw (1928) found it in teeth of the Strandlooper and

Boskop peoples in South Africa, while the modern Bantu and Bushmen have cynodont teeth. Taurodont teeth are found in Heidelberg man and are frequent in Neanderthal man. They are also known to occur occasionally in modern Europeans, Amerindians and Eskimos, and are frequent in the South African races. Shaw regards their appearance here as a result of crossing with Australoid and Boskopoid peoples, taurodontism being perhaps recessive in the hybrids, about 30 per cent of whom show the condition in varying degrees. See also Galloway (1937). Taurodontism is best defined (Keith) as a tendency of the pulp cavity to enlarge at the expense of the roots. Weidenreich finds taurodontism characteristic of all fossil hominids, as well as the chimpanzee and especially the female orang utan.

From a study of the teeth and jaws of native races, both recent and prehistoric, Abel (1933) concludes that anomalies result from disharmonies between teeth and jaws in racial crosses. He cites various cases in crosses between Bushmen, Hottentots and Negroes, where disharmonies arise from new combinations of the genetic factors involved among people living in "natural" rather than "civilized" conditions of food, etc.

Shovel-shaped incisors (koilomorphy) is another primitive tooth character which has survived with different frequencies in modern races. From extensive observations, Hrdlička (1920) found them mainly in the upper but also in lower incisors. They are frequently found in American Indians and generally (*ca.* 95 per cent) in Mongolian races, fewer in Eskimos. In Melanesians they may be fully formed or absent. One-third to one-half of Hawaiians have shovel-shaped incisors. In whites they are rare (not over 1 per cent) and perhaps four times as frequent in Negroes. No careful study of their inheritance has been made. They were present in Paleolithic man and are found in Primates and other mammals.

In a recent study of the Pa Miao, a native people in Kweichow province, S. W. China, Woo (1942) finds about 73% with shovel-shaped upper medial incisors, whereas in Chinese the frequency is *ca.* 90%.

LITERATURE

Abel, W. 1933. Zähne und Kiefer in ihren Wechselbeziehungen bei Buschmännern; Hottentotten, Negern und deren Bastarden. *Zeits. f. Morph. u. Anthrop.* 31:314–361. Pls. 6.

Adams, S. 1932. A note on an unusual pedigree. *Eugen. Rev.* 23:334–336.

Adamson, W. B. 1935. Psoriasis as a possible allergic manifestation. *J. Allergy* 6:294–297.

Allworthy, S. W. 1909. Notes on a case of excessive growth of beard. *Brit. J. Derm.* 21:152–153. Pl. 1.

Anderson, McCall. 1883. On a unique case of hereditary trichorexis nodosa. *Lancet* ii. 140–141. Fig. 1.

Archer, B. W. C. 1927. Multiple cavernous angiomata of the sweat glands associated with hemiplegia. *Lancet* ii. 595–596.

Ashley-Montagu, M. F. 1933. The dentition of identical twins with particular reference to an identical pathological condition. *Human Biol.* 5:629–645. Figs. 9.

———. 1940. The significance of the variability of the upper lateral incisor teeth in man. *Human Biol.* 12:323–358. Figs. 2.

Aycock, W. L. 1941. Familial susceptibility to leprosy. *Am. J. Med. Sci.* 201:450–466.

Bachrach, F. H. & Young, M. 1927. A comparison of the degree of resemblance in dental characters shown in pairs of twins of identical and fraternal types. *Brit. Dent. J.* 48:1293–1304.

Badger, L. F. 1942. The possible relation of nutrition to leprosy. *Proc. 6th Pacific Sci. Congr.* 5:965–971.

Baisch, A. 1931. Anonychia congenita, kombiniert mit Polydaktylie und verzörgertem abnormen Zahndurchbruch. *Deut. Zeits. f. Chir.* 232:450–457. Figs. 5.

Baker, Henry. 1755. A supplement to the account of a distempered skin, published in the 424th number of the Philosophical Transactions. *Phil. Trans. Roy. Soc.* 42:21–24.

Bamber, G. 1935. Epidermolysis bullosa hereditaria simplex. *Proc. Roy. Soc. Med.* 29:94–95.

*Bampton. 1914. *6th Internat. Dental Congr.* London. P. 167.

Barber, H. W. 1929. On the relationship of dermatology to other branches of medicine. *Trans. Med. Soc. Lond.* 52:165–248.

Barrett, A. M. 1919. Hereditary occurrence of hypothyroidism with dystrophies of the nails and hair. *Arch. of Neur. & Psychiat.* 2:628–637. Figs. 4.

Beigel, H. 1868. Ueber abnorme Haarentwicklung beim Menschen. *Arch. f. path. Anat. u. Physiol.* 44:418–427. Pls. 2.

Berglund, V. 1924. Sechs Fälle von Hypotrichosis in einer Familie. *Hereditas* 5:44–48.

Bernstein, M. M. & Burks, B. S. 1942. The incidence and Mendelian transmission of mid-digital hair in man. *J. Hered.* 33:45–53. Figs. 4.

Bissell, G. W. & Williams, R. H. 1945. Hirsutism in females. *Ann. Int. Med.* 22:773–806. Figs. 9.

Bloch. 1925. Hypertrichosis congenita partialis hereditaria. *Münch. Med. Wochens.* 72:1947.

Bloom, C. J. 1931. Hereditary juvenile pellagra, a résumé of the literature. *Ann. Int. Med.* 4:817–840.

Bloom, D. 1931. Inheritance of keratosis. *Eugen. News* 16:210–211.

Bloom, D. & Abramowitz, E. W. 1943. Porokeratosis Mibelli. *Arch. of Derm. & Syph.* 47:1–15. Figs. 8.

Bovero, A. 1929. Chiandole sebacee libere della mucosa geniana in varie razze umana. *Fol. Clin. et Biol. São Paulo* 1:34–41.

Brain, R. T. 1937. Familial ectodermal defect. *Proc. Roy. Soc. Med.* 31:69–70.

———. 1938. Alopecia congenita: minor ectodermal defect. *Proc. Roy. Soc. Med.* 32:87–88.

Brauer, A. 1913. Über eine besondere Form des hereditären Keratoms. (Keratoma dissipatum hereditarium palmare et plantare.) *Arch. f. Derm. u. Syph.* 114:211–236. Pls. 2.

———. 1929. Hereditärer symmetrischer systematisierter Naevus aplasticus bei 38 Personen. *Derm. Wochens.* 89:1163–1168. Figs. 3.

Brekhus, P. J., Oliver, C. P. & Montelius, G. 1944. A study of the pattern and combinations of congenitally missing teeth in man. *J. Dent. Res.* 23:117–131. Figs. 8.

Brushfield, T., & Wyatt, W. 1926. Epiloia. *Brit. Journ. Children's Diseases,* 23:178–185. Figs. 7.

Bulloch, W. 1909. Chronic hereditary trophoedema. *Treas. Human Inher.* pt. i. 32–38. Pls. 2.

Bunting, R. W. 1933. Recent developments in the study of dental caries. *Science* 78:419–424.

Cady, L. D. & Trotter, M. 1922. A study of ringed hair. *Arch. of Derm. & Syph.* 6:301–317.

Campbell, C. G. 1929. The inheritance of anodontia. *Eugen. News* 14:114–117.

———. 1934. Congenitally missing upper lateral incisor teeth. *Dent. Cosmos* 76:459–471.

Cartledge, J. L. & Myers, V. W. 1943. Inherited foot-blistering in an American family. *J. Hered.* 34:24.

Castle, W. F. R. 1925. Epidermolysis bullosa (five cases). *Proc. Roy. Soc. Med.* 18: (Sect. Derm.) 25–26.

Černy, C. 1924. A case of anodontia. *Dent. Cosmos* 66:583.

Chipps, H. D. 1932. Anodontia. *Dental Cosmos* 74:612–613. Figs. 2.

Cipollaro, A. C. 1930. Koilonychia. *N. Y. State J. Med.* 30:380–385.

Clark, F. H. & Clark, C. S. 1933. Absence of tooth enamel. *J. Hered.* 24:425–429. Figs. 5.

Clemente, L. S. 1928. A claw-fingered family. *J. Hered.* 19:528–536. Figs. 6.

Clouston, H. R. 1929. A hereditary ectodermal dystrophy. *Can. Med. Assn. J.* 21:18–31. Figs. 13.

———. 1939. The major forms of hereditary ectodermal dysplasia. *Can. Med. Assn. J.* 40:1–7. Figs. 4.

Cockayne, E. A. 1933. *Inherited Abnormalities of the Skin and Its Appendages.* Oxford Press. Pp. 394.

———. 1938. Recurrent bullous eruption of the feet. *Brit. J. Derm. & Syph.* 50:358–362.

*Coello, J. R. M. 1943. Displasia hereditaria del ectodermo a tipo anhidrotico. *Vida Nueva (Habana)* 52:156–161.

Cole, L. J. 1919. A defect of hair and teeth in cattle, probably hereditary. *J. Hered.* 10:303–306. Figs. 5.

Cole, L. J. & Owen, R. D. 1944. Naked pigeons. *J. Hered.* 35:2–7. Figs. 4.

Corson, E. F. 1934. Nevus flammeus nuchae: its occurrence and abnormalities. *Am. J. Med. Sci.* 187:121–124. Fig. 1.

Crawford, J. 1854. *Journal of an Embassy from the Governor General of India to the Court of Ava.* London. 2nd ed. Vol. 1. P. 318.

Crew, F. A. E. 1922. Hackleless or bare-necked fowls. *Nat. Poult. Journ.* P. 194.

Crosman, A. M. 1927. Inheritance of abnormalities in teeth. *J. Hered.* 18:368–370.

*Csörsz, K. 1928. Rezessiv geschlechtsgebundene Vererbung bei Ichthyosis. *Monatschr. ungar. Med.* 2:180–187.

Dahlberg, A. A. 1945. The paramolar tubercle (Bolk). *Am. J. Phys. Anthrop.* N. S. 3:97–103. Figs. 6.

Danforth, C. H. 1921. Distribution of hair on the digits in man. *Amer. Journ. Phys. Anthrop.* 4:189–204.

———. 1925. Studies on hair, with special reference to hypertrichosis. *Arch. Derm. & Syph.* Vols. 11 and 12. Also *Amer. Med. Assn.* Pp. 152, figs. 64.

———. 1928. A case of alopecia in the fowl. *J. Hered.* 29:547–550. Figs. 3.

Davenport, C. B. 1914. The Bare-necks. *Journ. Hered.* 5:374. Fig. 1.

———. 1916. The hereditary factor in pellagra. *Arch. Int. Med.* 18:4–31.

David, Lorna T. 1932. The external expression and comparative dermal histology of hereditary hairlessness in mammals. *Zeits. f. Zellforsch. u. Mikro. Anat.* 14:616–719. Figs. 48.

Davies, T. & McGregor, D. 1942. A case of hologynic inheritance of ichthyosis vulgaris. *Brit. J. Derm.* 54:121–122.

Dean, C. H. 1921. A case of congenital ichthyosis. *J. Am. Med. Assn.* 77:465.

De Bray, M. & Sainton, J. 1930. Un case de kératodermie palmaire et plantaire symétrique congénitale et héréditaire. *Bull. et Mém. Soc. Méd. d. Hôp. de Paris.* 46:226–227.

Decking, E. 1926. Ephelidenuntersuchungen zum Ausbau der Siemenschen Methode zur Diagnose der Eineiigkeit. *Münch. Med. Wochens.* 73:1188–1190.

Denaro, S. J. 1944. The inheritance of nevi. *J. Hered.* 35:215–218.

Denny-Brown, D. 1938. Adenoma sebaceum, without epilepsy, in a woman: epilepsy without adenoma sebaceum in her son. *Proc. Roy. Soc. Med.* 31:717–718.

Dietz, V. H. 1944. A common morphotrophic factor, the carabelli cusps. *J. Am. Dent. Assn.* 31:784–798. Figs. 3.

Dowling, G. B. 1930. Atrophic lesions on joints of hands and feet. *Proc. Roy. Soc. Med.* 24:102.

Dressler, M. 1938. Boeck'sche Krankheit der Lungen bei Geschwistern. *Schweiz. Med. Wochens.* 68:417–422. Figs. 6.

*Drewes. 1939. Hereditäre Elephantiasis. *Der Erbarzt* 6:70–71.

Duerden, J. S. 1918. Some results of ostrich investigations. *S. Afr. J. Sci.* Pp. 38, pls. 4, figs. 4.

———. 1919. Crossing the N. African and S. African ostrich. *J. Genet.* 8:155–198. Pl. 1, figs. 2.

East, B. R. 1942. Geography and tooth decay. *Sci. Mon.* 55:582.

Ehrhardt, S. 1932. Ringelhaare in der Familie E. *Münch. Med. Wochens.* 79:949–951. Figs. 5.

Estabrook, A. H. 1928. A family with birthmarks (naevus spilus) for five generations. *Eugen. News* 13:90–92.

Evans, J. J. & P. J. 1939. Ocular changes (especially optic atrophy and haemangioma of choroid) associated with naevus flammeus. *Brit. J. Ophth.* 23:95–105.

Faber, H. K. & Lusignan, H. R. 1933. Hereditary elephantiasis. *Am. J. Dis. Child.* 46:816–825.

Fantham, H. B. 1924. Heredity in man: its importance both biologically and educationally. *S. Afr. J. Sci.* 21:498–527. Figs. 15.

———. 1925. Some factors in eugenics, together with notes on some S. African cases. *S. Afr. J. Sci.* 22:400–424. Figs. 4.

Felsher, Z. 1944. Hereditary ectodermal dysplasia. *Arch. of Derm. & Syph.* 49:410–414.

Fenner, F. 1942. The mid-dorsal hair whorl in an Australian of European ancestry. *J. Anat.* 76:356–358. Figs. 2.

Finn, S. B. 1938. Hereditary opalescent dentin. I. An analysis of the literature on hereditary anomalies of tooth color. *J. Am. Dent. Assn.* 25:1240–1249.

Fischer, E. 1910. Ein Fall von erblicher Haararmut und die Art ihrer Vererbung. *Arch. f. Rass. Ges. Biol.* 7:50–56.

Fischer, F. 1925. Studien über Vererbung von Hautkrankheiten. VIII. *Arch. f. Rass. Ges. Biol.* 16:404–413.

Fleischmann, O. 1935. Die Bedeutung der Anidrosis hypotrichotica in erblicher und klinischer Hinsicht. *Arch. f. Rass. Ges. Biol.* 29:257–277. Figs. 15.

Ford, E. 1940. A destructive disease of the skin in natives of Papua and North Australia. *Med. J. Australia* 2:668–669. Fig. 1.

Ford, N. & Mason, A. D. 1943. Heredity as a factor in malocclusion. *J. Hered.* 34:57–64.

Fox, E. C. 1940. Report of cases of onycholysis. *Arch. Derm. & Syph.* 41:98.

Frank, J. & Sandford, W. C. 1891. A remarkable case of skin disease. *Am. J. Med. Sci.* 102:164–168. Figs. 2.

Frank, S. B. 1943. Recurrent bullous eruption of the feet. *Arch. of Derm. & Syph.* 47:327–334. Figs. 4.

Franklin, J. 1938. Pachyonychia congenita (Jadassohn and Lewandowski). *Proc. Roy. Soc. Med.* 32:263–265. Figs. 2.

Franks, A. G. & Davis, M. I. J. 1943. Epidermolysis bullosa. *Arch. of Derm. & Syph.* 47:647–650.

Frets, G. P. 1929. Ichthyosis generalis, een geval van geschlachtsgebonden erfelijkheid. *Genetica* 11:451–452.

Friedenthal, H. 1908. *Das Haarkleid des Menschen.* Berlin. Pp. 179, pls. 43.

Fuhs, H. 1925. Über Naevus multiplex Pringle (Adenoma sebaceum). *Arch. f. Derm. u. Syph.* 148:509–515.

———. 1930. Der Erbgang der Keratosis palmo-plantaris papulosa. *Arch. f. Derm. u. Syph.* 160:52–55.

Gahan, E. 1943. Incidence of psoriasis among the population at large. *Arch. of Derm. & Syph.* 48:305.

Galloway, A. 1937. The skeletal remains of Mapungubwe. In Fouché, L. *Mapungubwe.* Pp. 183. Cambridge Press.

Garb, J. & Stone, M. J. 1942. Keloids. *Am. J. Surgery* 58:315–335. Figs. 24.

Gardner, T. A. 1927. Six generations of congenitally missing teeth. *Dent. Cosmos* 69:1041–1045. Figs. 8.

Garnier, G. 1945. Relation of the gonadal hormones to certain dermatoses. *Nature* 156:339–340.

Gates, R. R. 1942. Heredity and environment in human genetics. *Current Sci.* (India) 11:127–134.

Gates, W. H. & Pullig, T. 1945. The linkage of dominant white spotting with hairless in the house mouse. *Genetics* 30:4 (Abst.).

Gillespie, J. B. 1937. Congenital and familial alopecia totalis. *Am. J. Dis. Child.* 53:132–136. Fig. 1.

Glaser, S. 1934. Sweat glands in the negro and the European. *Am. J. Phys. Anthrop.* 18:371–376.

Glass, L. C. & Yost, D. H. 1939. Inherited inability to sweat. *J. Hered.* 30:477–478.

Goblirsch, A. W. 1930. A study of third molar teeth. *J. Am. Dent. Assn.* 17:1849–1854.

Goeckermann, W. H. 1920. Congenital ectodermal defect, with report of a case. *Arch. of Derm. & Syph.* 1:396–412. Figs. 12.

Good, C. K. & Garb, J. 1943. Symmetric nevi of face, tuberous sclerosis, epilepsy and fibromatous growth on scalp. *Arch. of Derm. & Syph.* 47:197–215. Figs. 8.

Görl, L. 1934. Vitiligo, alopecia areata. *Derm. Wochens.* 98:58.

Gordon, W. H. & Jamieson, R. C. 1931. Hereditary ectodermal dysplasia of the anhidrotic type. *Ann. Int. Med.* 5:358–370. Figs. 6.

Gossage, A. M. 1908. The inheritance of certain human abnormalities. *Quart. J. Med.* 1:331–347.

Gray, A. M. H. 1920. Case of generalized rodent ulcer. *Proc. Roy. Soc. Med.* 13: Sect. Derm. 68–70. Fig. 1.

Greenberg, S. I. 1944. Epidermolysis bullosa. *Arch. of Derm. & Syph.* 49:333–334.

Greenwood, A. W. 1927. The "hackleless" fowl. *Proc. Roy. Phys. Soc.* (Edinb.), 21:123–129. Figs. 4.

Greep, R. O. 1941. An hereditary absence of the incisor teeth. *J. Hered.* 32:397–398. Fig. 1.

Gregory, W. K. 1920–1921. On the origin and evolution of the human dentition. *J. Dent. Res.* Vols. 2 and 3.

Griffith, G. M. 1936. Hydroa aestivale. *Proc. Roy. Soc. Med.* 29:1638–1639.

Grüneberg, H. 1936. Two independent inherited tooth anomalies in one family. *J. Hered.* 27:224–228. Figs. 3.

Guilford, H. S. 1883. A dental anomaly. *Dental Cosmos* 25:113–118.

Günther, H. 1932. Beobachtungen von Keratoma hereditarium planoplantare (Typus Unna). *Arch. f. Derm. u. Syph.* 165:475–489. Figs. 2.

Gunther, M. & Penrose, L. S. 1935. The genetics of epiloia. *J. Genet.* 31:413–430.

Guy, W. H. 1927. Epidermolysis bullosa. *Arch. of Derm. & Syph.* 15:30–42. Figs. 11.

Haldane, J. B. S. 1937. A probable new sex-linked dominant in man. *J. Hered.* 28:58–60.

Haldane, J. B. S. & Poole, R. 1942. A new pedigree of recurrent bullous eruptions of the feet. *J. Hered.* 33:17–18.

Hecht, H. 1930. Erblichkeit bei Hautkrankheiten. *Derm. Wochens.* 90:533–537.

———. 1930. Keratosis palmoplantaris diffusa hereditaria. *Derm. Wochens.* 91:1022–1027. Figs. 2.

Heggs, G. M. 1936. Poikilodermia with polydactyly. *Proc. Roy. Soc. Med.* 29:717–720. Figs. 4.

Hellier, F. F. 1937. Granulosis rubra nasi in a mother and daughter. *Brit. Med. J.* ii. 1068.

Hellier, F. F., Astbury, W. T. and Bell, F. O. 1940. A case of pili torti, with a discussion of the molecular structure of the condition and its relationship to monilethrix. *Brit. J. Derm.* 52:173–182.

Henckel, K. O. 1935. Hypotrichosis congenita bei eineiigen Drillingen. *Klin. Wochens.* 14:428–429. Figs. 2.

*Hershan. 1927. *Zeits. f. Sexualwiss.* 14:161.

Hess, J. H. & Schultz, O. T. 1921. Keratosis diffusa fetalis (ichthyosis congenita). *Am. J. Ch. Dis.* 21:357–388. Figs. 12.

Heuck, O. 1924. Studien über Vererbung von Hautkrankheiten. VII. Monilotrichosis. *Arch. f. Derm. u. Syph.* 147:196–200.

Hill, J. H. 1881. Hairless Australian aboriginals. *Brit. Med. J.* i. 177.

Hobbs, M. E. 1935. Hereditary onychial dysplasia. *Am. J. Med. Sci.* 190:200–206. Figs. 5.

Hodge, H. C. & Finn, S. B. 1938. Hereditary opalescent dentin. *J. Hered.* 29:359–364. Figs. 3.

Hodge, H. C. *et al.* 1940. III. Histological, chemical and physical studies. *J. Dent. Res.* 19:521–536. Figs. 19.

Hoffmann, E. 1926. Über den Erbgang bei Epidermolysis bullosa hereditaria. *Arch. f. Rass. u. Ges.-Biol.* 18:353–368.

Hope, W. B. & French, H. 1908. Persistent hereditary oedema of the legs with acute exacerbations. Milroy's disease. *Quart. Journ. Med.* i. 312–330. Pls. 2.

Hrdlička, A. 1920. Shovel-shaped teeth. *Am. J. Phys. Anthrop.* 3:429–465. Pls. 6.

Huizenga, L. S. 1942. The unchanging distribution of leprosy in China. *Proc. 6th Pac. Sci. Congr.* 5:947–951.

Hunt, H. R., Hoppert, C. A. & Erwin, W. G. 1944. Inheritance of susceptibility to caries in albino rats (*Mus norvegicus*). *J. Dent. Res.* 23:385–401.

Huskins, C. L. 1930. On the inheritance of an anomaly of human dentition. *J. Hered.* 21:279–282. Fig. 1.

Hutchinson, J. 1886. Congenital absence of hair and mammary glands. *Medico-Chir. Trans.* 69:473–477.

Hutchinson, J. 1891. On the tendency to flush as a cause of morbid changes. *Brit. J. Derm.* 3:1–7. Pl. 1.

Hutt, F. B. 1935. An earlier record of the toothless men of Sind. *J. Hered.* 26:65–66.

Ihre, B. 1932. Case of anadontia. *Acta Med. Scand.* 79:23–31. Figs. 3.

Ingram, J. T. & Oldfield, M. C. 1937. Hereditary sebaceous cysts. *Brit. Med. J.* i. 960–963. Pls. 2.

Jacob, F. H. & Fulton, A. 1905. Keratosis palmaris et plantaris in five generations. *Brit. Med. J.* ii. 125.

Jacobsen, A. W. 1928. Hereditary dystrophy of the hair and nails. *J. Am. Med. Assn.* 90:686–689. Figs. 11.

Jenness, Diamond. 1928. *The People of the Twilight.* New York: Macmillan. Pp. 247.

Jenny, E. 1927. Über eine letal verlaufende Form von Epidermolysis bullosa hereditaria beim Säugling. *Zeits. f. Kinderhlk.* 43:138–148.

Joachim, H. 1936. Hereditary dystrophy of the hair and nails in six generations. *Ann. Int. Med.* 10:400–402. Figs. 2.

Johnson, A. LeRoy. 1940. The constitutional factor in skull form and dental occlusion. *Am. J. Orthodont.* 26:627–663. Figs. 29.

Jöhr, A. C. 1934. Reduktionserscheinungen an den oberen seitlichen Schneidezähnen dominant gehäuft in einem Schwyzer Bergdorf. *Arch. J. Klaus-Stift.* 9:73–130. Figs. 3.

Jones, E. 1924. The occurrence of an eye and of a tooth abnormality in a line of albino rats. *Anat. Rec.* 29:142.

Jones, W. A. 1933. Familial multilocular cystic disease of the jaws. *Am. J. Cancer.* 17:946–950. Figs. 7.

*Junghanns. 1922. *Derm. Wochens.* 74:334.

*Juon, M. 1942. Eine Beobachtung familiären Auftretens von Pili anulati. *Dermatologia (Basel)* 86:117–122.

Kadner, A. 1933. Identification by proof of inherited jaws of two children exchanged after birth. *Internat. J. Orthodont.* 19:153–159. Figs. 3.

Keeler, C. E. 1935. Heredity in dentistry. *Dental Cosmos* 77:1147–1163.

Keeler, C. E. & Short, R. 1934. Hereditary absence of upper lateral incisors. *J. Hered.* 25:391–392. Figs. 2.

Kislovsky, D. A. 1928. Naked — a recessive mutation in the rabbit. *Journ. Hered.* 19:438–439. Figs. 3.

Knorre, G. V. 1936. Ein angeborener Ektodermaldefekt und seine Vererbung. *Zeits. f. Vererb. u. Konst.* 20:66–72. Figs. 6.

Kooistra, H. P. 1942. Pilonidal sinuses. *Am. J. Surgery* 55:3–17. Figs. 6.

Korkhaus, G. 1930. Anthropologic and odontologic studies in twins. *Internat. J. Orthodont.* 16:640–647. Figs. 22.

———. 1931. Die Vererbung der Zahnfarbe. *Zeits. f. Konst-lehre* 15:127–133. Figs. 3.

Lane, J. E. 1929. Erythema palmare hereditarium (red palms). *Arch. of Derm. & Syph.* 20:445–448.

Leber, Ruth. 1936. Über eine Familie mit erblichem universellem Melanismus. *Zeits. f. Kinderhlk.* 58:142–147. Fig. 1.

LeDouble, A. F. & Houssay, F. 1912. *Les Velus.* Paris.

Lehr, M. H. 1939. A new inherited skin defect in man. *J. Hered.* 30:331–334. Figs. 3.

Lenz, F. 1926. Über die Erblichkeit der Müttermäler auf Grund von Untersuchungen an 300 Zwillingspaaren. *Zeits. f. Abst. u. Vererb.* 41:119–121.

Lerner, C. 1940. Hereditary influences in psoriasis. *J. Invest. Derm.* 3:347–356.

Leven, L. 1928. Zur Vererbung der Psoriasis. *Arch. f. Rass. Ges. Biol.* 20:175–176.

Lettsom, Dr. 1792. *Mem. Med. Soc. Lond.* 3:515–517.

Levit, S. G. 1931. On the heredity of atheroma. *J. Hered.* 22:2–5. Figs. 2.

———. 1936. The problem of dominance in man. *J. Genet.* 33:411–434.

Lichstein, J. & Solis-Cohen, L. 1943. Familial tuberous sclerosis (epiloia) without adenoma sebaceum. *J. Am. Med. Assn.* 122:429–432. Figs. 5.

Liu, C. H. 1937. On a hairy man of China. *Zeits. f. Rassenk.* 6:339–340. Fig. 1.

Loveman, A. B. & Graham, P. V. 1941. Acrokeratosis verruciformis (Kopf). *Arch. of Derm. & Syph.* 43:971–979. Figs. 2.

Lowe, J. 1942. Variations in leprosy and its epidemiology seen in different countries. *Proc. 6th Pacific Sci. Congr.* 5:921–926.

Lucas, R. C. 1888. On the congenital absence of an upper lateral incisor tooth as a forerunner of harelip and cleft palate. *Trans. Clin. Soc. Lond.* 21:64–66.

———. 1904. On an ill-developed upper lateral incisor tooth as a forerunner of harelip, and cleft palate. *Brit. J. Ch. Dis.* 1:483–489.

Lundborg, H. 1927. Geschlechtsgebundene Vererbung von Ichthyosis simplex vulgaris in einer Schwedischen Bauernsippe. *Hereditas* 9:45–48.

*Luschan, von. 1907. *Zeits. f. Ethnol.* 39:425.

*Lusha. 1923. *Zentlbl. f. Haut- u. Geschlechtskh.* 8:509.

MacCormac, H. 1939. Schaumann's disease in two sisters. *Proc. Roy. Soc. Med.* 32:724.

McCracken, I. E. 1931. *Brit. Med. J.* ii. 225.

McFeeters, J. W. 1939. Morbid inheritance in an isolated community. *Brit. Med. J.* i. 218–220.

McGuire, J. & Zeek, Pearl. 1932. Pathogenesis of chronic hereditary edema of extremities (Milroy's disease). *J. Am. Med. Assn.* 98:870–873. Figs. 6.

Machin, J. 1733. An extract from the minutes of the Royal Society, March 16, 1731, containing an uncommon case. *Phil. Trans. Roy. Soc.* 37:299–301. Figs. 3.

MacKee, G. M. & Andrews, G. C. 1924. Congenital ectodermal defect. *Arch. of Derm. & Syph.* 10:673–701. Figs. 12.

MacLeod, J. M. H. 1909. Three cases of "ichthyosis follicularis" associated with baldness. *Brit. J. Derm.* 21:165–189. Figs. 3.

Macklin, M. T. 1936. Xeroderma pigmentosum an inherited disease due to recessive determiners. *Arch. of Derm. & Syph.* 34:656–675.

———. 1938. Absent tooth enamel. *Eugen. News* 23:28–29. Figs. 2.

Macklin, M. T. 1944. Xeroderma pigmentosum. *Arch. of Derm. & Syph.* 49:157–171.

McQuillan, J. H. 1870. Hereditary transmission of dental irregularities *Dental Cosmos* 12:27–29, 73–75, 193–195.

Magitot, M. 1892. Moulages de doigts recueillis sur les cagots de Salies-de-Béarn. *Bull. Soc. d'Anthrop. de Paris* 3:553–572. Figs. 2.

Manson, J. S. 1928. *Observations on Human Heredity.* London: Lewis. Pp. 84, pls. 8, figs. 19.

Marcuse, M. 1929. Zur Erblichkeit der Psoriasis und der Cholezystitis und über die Verbreitung beider Leiden in einer Familie. *Arch. f. Rass. Ges. Biol.* 22:50–51.

*Marquez, M. 1928. *Zentlbl. f. Haut. u. Geschlechtskh.* 22:517.

———. 1928. Las hipertricosis localizadas y especialmente la hipertricofridia. *Siglo Med.* 82:253, 279.

Martin, A. N. 1938. Primera observación española de pili torti familiar. *Actas Dermo-Sif.* 30:139–147. Figs. 4.

Martin, P. J. 1818. Case of hereditary ichthyosis. *Med. Chirurg. Trans.* 9:52–55. Pls. 2.

Mayr, J. K. 1935. Zur Vererbbarkeit des Ekzems. *Arch. f. Dermat.* 171:612–621. Figs. 3.

Mehney, G. H. 1937. Naevus flammeus (of face) associated with glaucoma. *Arch. of Ophth.* 17:1018–1023. Figs. 3.

*Meige, Henry. 1898. Dystrophie oedémateuse héréditaire. *Presse Méd.* 6:341–343. Figs. 5.

Meirowsky, E. 1942. Moles and malformations of the skin in their relationship to inheritance and phyogenesis. *Brit. J. Dermat.* 54:99–121, 129–153. Figs. 11.

Meirowsky, E. & Bruck, W. 1921. Über die Vererbung und die Aetiologie der Muttermäler. *Münch. Med. Wochens.* 68. ii. 1048–1049.

Meirowsky, E. & Leven, L. 1921. Tierzeichnung, Menschenscheckung und Systematization der Muttermäler. Berlin. Pp. 79, pls. 19.

Michael, J. C. 1933. Keratoderma disseminatum palmaris et plantaris. Its mode of inheritance. *Arch. of Derm. & Syph.* 27:78–88. Figs. 2.

Michelson, P. 1885. Zum Capitel der Hypertrichosis. *Virchow's Arch.* 100:66–80. Pl. 1.

Miescher, 1925. Drei Fälle von familiäre Keratose der Haut und Schleimhäute, etc. *Derm. Zeits.* 44:189–200.

Miklucho-Maclay, N. 1881. Haarlose Australier. *Zeits. f. Ethnol.* 13: 143–149. Pl. 1.

Miller, M. A. 1941. An inherited dental anomaly in a Japanese family. *J. Hered.* 32:313–314. Figs. 2.

Milroy, W. F. 1892. An undescribed variety of hereditary oedema. *New York Med. J.* 56:506–508.

———. 1928. Chronic hereditary edema: Milroy's disease. *J. Am. Med. Assn.* 91:1172–1175. Figs. 3.

Mohr, O. L. 1926. Über Letalfaktoren mit Berücksichtigung ihres Verhaltens bei Haustieren und beim Menschen. *Zeits. f. Abst. u. Vererb.* 41:59–109. Pl. 1, figs. 10.

Mohr, O. L. & Wriedt, C. 1928. Hairless, a new recessive lethal in cattle. *J. Genet.* 19:315–336. Pls. 2, fig. 1.

*Monteiro. 1921. *Bull. et Mém. Soc. Anthrop. de Paris.* 12:154.

Moore, G. R. 1924. A case of agenesia of enamel. *Dent. Cosmos* 66:582–583.

Mullen, L. M. 1936. Ichthyosis. *Can. Med. Assn. J.* 34:430.

Muncey, E. B. 1916. A study of the heredity of pellagra in Spartanburg County, South Carolina. *Arch. Int. Med.* 18:32–72.

Munro, T. A. 1937. Hereditary sebaceous cysts. *J. Genet.* 35:61–72.

Murray, F. A. 1921. Congenital anomalies of the nails. *Brit. J. Derm. & Syph.* 33:409–410. Figs. 4.

Nager, G. 1925. Familiäres Auftreten von Epidermolysis bullosa dystrophica hereditaria. *Schweiz. Med. Wochens.* 6:306–307.

Nonne, M. 1891. Vier Fälle von Elephantiasis congenita hereditaria. *Virchow's Arch.* 125:189–196. Pls. 2.

Nordby, J. E. 1933. Congenital melanotic skin tumors in swine. *J. Hered.* 24:361–364. Figs. 2.

Oliver, E. A. & Bluefarb, S. M. 1944. Nevus striatus symmetricus unguis. *Arch. of Derm. & Syph.* 49:190. Figs. 2.

Oliver, E. A. & Gilbert, N. C. 1926. Congenital alopecia. *Arch. of Derm. & Syph.* 13:359–373. Figs. 5.

Oliver, W. J. 1925. Congenital atrophy of the hair and nails. *Arch. of Derm. & Syph.* 10:347.

Oppenheim. 1937. Leukonychia totalis bei Vater und Sohn. *Zentlbl. f. Haut- u. Geschlechtskr.* 57:9.

Orban-Vadja, A. 1925. Familiäre Ichthyosis. *Zentlbl. f. Hautkrankh.* 17:627.

Orel, H. 1928. Ueber eine Familie mit erblicher Onychogryphosis. *Arch. f. Rass. Ges. Biol.* 20:169–175. Fig. 1.

———. 1929. Die Vererbung der Ichthyosis congenita und der Ichthyosis vulgaris. *Zeits. f. Kinderhlk.* 2:350.

Osborn, D. 1916. Inheritance of baldness. *J. Hered.* 7:347–355. Figs. 9.

Ovazza, V. E. 1922. Sull'assenza ereditaria degli incisivi. *La Stomatol.* 20:21–23.

Pappworth, M. H. 1941. Cyclical mucosal ulceration. *Brit. Med. J.* i. 271–273.

Peck, S. M., Glick, A. W., Sobotka, H. & Chargin, L. 1943. Vitamin A studies in cases of keratosis follicularis (Darier's disease). *Arch. of Derm. & Syph.* 48:17–31. Figs. 8.

Penrose, L. S. 1936. Autosomal mutation and modification in man with special reference to mental defect. *Ann. of Eugen.* 7:1–16.

Pettigrew, 1833. Phenomenon of the skin. *Lancet* ii. 146–147.

Pfanner, K. 1930. Statistische Untersuchungen über die Vererbung von Zahncaries. *Arch. J. Klaus-Stift.* 5:259–302.

Pflüger, H. 1929. Über erbliche Schmelzunterentwicklung. *Klin. Wochens.* 8:330.

Pick, E. 1925. Familiäre Ichthyosis. *Zentlbl. f. Haut. u. Geschlkh* 16:521.

Pitts, A. T. 1923. Congenital absence of teeth in three members of a family. *Proc. Roy. Soc. Med.* 16: Child. Sect. 44–45.

Price, Weston A. 1923. *Dental Infections, Oral and Systemic.* Cleveland: Vols. 2, pp. 673 + 471.

Pringle, J. J. 1913. An angiokeratomatous family. *Proc. Roy. Soc. Med.* 6. i. Derm. Sect. P. 76.

Ramorino, C. 1924. Dell' ittiosi familiare. *Giorn. Ital. delle Malatti Veneree* 65:616–622.

Redlich, E. 1926. Über physiologische Hypertrichose. *Zeits. f. Vererb. u. Konstit.* 12:740–757. Figs. 18.

Riebler, R. 1936. Über ein gemeinsames familiäres Vorkommen von Psoriasis, Fettsucht und Struma. *Klin. Wochens.* 15:864–866.

Riecke, E. 1900. Ueber Ichthyosis congenita. *Arch. f. Derm. u. Syph.* 54:289–340. Pls. 6.

Roberts, E. 1929. The inheritance of anhidrosis associated with anadontia. *J. Am. Med. Assn.* 93:277–279. Figs. 13.

Roberts, E. & Thomas, L. C. 1930. Hypotrichosis: the inheritance of monilethrix. *Eugenics* 3:20–25. Figs. 11.

Roberts, E. & Schour, J. 1939. Hereditary opalescent dentine (dentinogenesis imperfecta). *Am. J. Orthodont.* 25:267–276. Figs. 10.

Rolleston, H. D. 1902. Persistent hereditary oedema of the lower limbs. *Lancet* ii. 805–807. Fig. 1.

Rushton, M. A. 1934. A case of anidrotic ectodermal dysplasia showing extensive dental defect. *Proc. Roy. Soc. Med.* 27:725–727. Figs. 3.

Rutherford, Marg. E. 1931. Three generations of inherited dental defect. *Brit. Med. J.* ii. 9–11.

Rygier-Cekalska, S. 1935. Über einen Fall von sogenannten gedrehten Haaren (Pili torti — Galewsky) bei Zwillingen. *Arch. f. Derm. u. Syph.* 173:75–77.

Sabouraud, R. 1892. Sur les cheveux moniliformes (trichorrexis et monilethrix). *Ann. de Derm. et Syph.* 3:781–793.

Schamberg, J. F. 1924. The known and the unknown about psoriasis. *J. Am. Med. Assn.* 83:1211–1214.

Scheidt, W. 1925. Einige Ergebnisse biologischer Familienerhebungen. *Arch. f. Rass. Ges. Biol.* 17:128–148. Pls. 4.

Schultz, A. H. 1926. Fetal growth of man and other Primates. *Quart. Rev. Biol.* 1:465–521. Figs. 20.

———. 1932. The hereditary tendency to eliminate the upper lateral incisors. *Human Biol.* 4:34–40. Figs. 5.

———. 1934. Inherited reductions in the dentition of man. *Human Biol.* 6:627–631. Figs. 2.

Schwartz, E. G. 1935. Hereditary ectodermal dysplasia of anhidrotic type. *South. Med. J.* 28:606–609. Figs. 4.

Sein, Min. 1936. Congenital and familial absence of hair from the whole surface of the body. *Lancet* 231:564–565.

Sergi, S. 1914. Missing teeth inherited. *J. Hered.* 5:559–560.

Shaw, J. C. M. 1927. Taurodont teeth in South African races. *J. Anat.* 62:476–498. Pl. 1, figs. 6.

Sherlock, E. B. 1911. *The Feeble-minded.* London.

Siemens, H. W. 1923. Atherom, — zugleich ein Beitrag zur Klinik der Epidermoide- und der Follicularen-cysten. *Arch. f. Derm. u. Syph.* 144:175–193.

———. 1925. Ueber einen, in der menschlichen Pathologie noch nicht beobachteten Vererbungsmodus: dominant-geschlechtsgebundene Vererbung. *Arch. f. Rass. Ges. Biol.* 17:47–61.

———. 1926. Die Vererbungspathologie der Akne. *Münch. Med. Wochens.* 73:1514–17.

———. 1930. Vererbungsforschung in der Dermatologie. *Arch. f. Derm. u. Syph.* 160:37–48.

Siemens, H. W. & Kohn, E. 1925. Studien über Vererbung von Hautkrankheiten. IX. Xeroderma pigmentosum. *Zeits. f. Abst. u. Vererb.* 38:1–61.

Siler, J. F., Garrison, P. E. & MacNeal, W. J. 1916. The incidence of pellagra in Spartanburg County, S. C., and the relation of the initial attack to race, sex and age. *Arch. Int. Med.* 18:173–211.

de Silva, P. C. C. 1939. Hereditary ectodermal dysplasia of anhydrotic type. *Quart. J. Med.* 32:97–113. Pls. 3.

Simpson, James Y. 1842. Antiquarian notices of leprosy and leper hospitals in Scotland and England. Part II. *Edinb. Med. & Surg. J.* 57:121–156. Part III. 57:394–429.

Sinha, S. 1918. Polydactylism and tooth color. *J. Hered.* 9:96.

Smith, A. G. 1934. Epidermolysis bullosa with psoriasis. *Lancet* 226:1393.

Smith, Jean. 1931. Hereditary ectodermal dysplasia. *Proc. Roy. Soc. Med.* 24:323–326. Figs. 2.

Snell, G. D. & Foley, F. 1932. Inheritance of ringed hair. *J. Hered.* 23:155–157. Figs. 2.

Snyder, L. H. & Yingling, H. C. 1935. The application of the gene-frequency method of analysis to sex-influenced factors, with special reference to baldness. *Hum. Biol.* 7:608–615.

Spindler, A. 1933. Zur Vererbung der Psoriasis vulgaris. *Arch. f. Derm. u. Syph.* 169:417–420.

Stauffer, J. & Simmons, I. 1942. Hyperkeratosis of the large toe-nails and sebaceous cysts. *J. Hered.* 33:285–288. Figs. 2.

Steggerda, M. 1930. The inheritance of thin skin. *Eugen. News* 15:148.

Stoddard, S. E. 1939. Catatrichy, a new character dependent upon a dominant autosomal gene. *J. Hered.* 30:543–545. Figs. 2.

Stokes, J. H. & King, A. D. 1932. Acne vulgaris: heredity in the etiologic background. *Arch. of Derm. & Syph.* 26:456–462. Peds. 5.

Stoll, K. L. 1936. Naevus flammeus and glaucoma. *Trans. Am. Acad. Ophth.* 41:534–544.

Stone, R. M. 1900. Keratolysis or "skin-shedding." *J. Am. Med. Assn.* 35:557–558. Figs. 2.

Sturkie, P. D. 1941. Studies on hereditary congenital baldness in the domestic fowl. *J. Morph.* 69:517–535. Figs. 9.

Sullivan, M. & Ellis, F. A. 1939. Epidermodysplasia verruciformis (Lewandowsky and Lutz). *Arch. of Derm. & Syph.* 40:422–432. Figs. 4.

Sumner, F. B. 1924. Hairless mice. *Journ. Hered.* 15:475–481. Figs. 3.

Sunderman, F. W. 1941. Persons lacking sweat glands. *Arch. Int. Med.* 67:846–854. Figs. 3.

Szodoray, L. 1939. Trichostasis spinulosa. *Dermatologica* 79:144–150. Figs. 4.

Taylor, R. W. 1888. Xeroderma pigmentosum and its relation to malignant new-growths of the skin. *Med. Record N. Y.* 33:261–269. Figs. 6.

Tendlau, B. 1902. Ueber angeborene und erworbene Atrophia cutis idiopathica. *Virchow's Arch.* 167:465–490.

Thadani, K. T. 1921. A toothless type of man. *J. Hered.* 12:87–88.

———. 1934. The toothless man of Sind. *J. Hered.* 25:483–484. Fig. 1.

Thin, Geo. 1892. On the origin and spread of leprosy at Parcent in Spain. *Lancet* i. 134–136.

Thompson, H. B. 1928. Hereditary dystrophy of the nails. *J. Am. Med. Assn.* 91:1547. Figs. 2.

Thomas, L. G. 1926. Five studies in human heredity. *Eugen. News* 11:150–153.

Thomson, M. S. & Wakeley, C. P. G. 1921. The harlequin foetus. *J. Obstet. & Gynec. Brit. Emp.* 28:190–203. Figs. 5.

Thorner, J. E. 1940. Alopecia totalis. *Endocrinology* 26:433–436. Figs. 9.

Thoroczkay, M. 1940. Osseous changes in hereditary epidermolysis bullosa. *Magyar röntgen. Köz.* 14:14–18.

Thurnam, J. 1848. Two cases in which the skin, hair and teeth were very imperfectly developed. *Trans. London Med. & Chir. Soc.* 31:71–82.

Tobias, N. 1925. Hereditary familial dystrophy of the nails. *J. Am. Med. Assn.* 84:1568–1569.

Tocantins, L. M. & Reimann, H. A. 1939. Perforating ulcers of feet, and osseous dystrophy. *J. Am. Med. Assn.* 112:2251–2255. Figs. 3.

Tomkinson, J. G. 1932. Monilethrix, a group of twenty-two cases. *Brit. Med. J.* ii. 1009–1011. Figs. 3.

———. 1935. Monilethrix, a second group of familial cases. *Brit. Med. J.* i. 526–527.

Tommasi, C. 1907. Ipertricosi auricolare famigliare. *Arch. psichiatr., neuropat., antropol., crim. e med. legale* 28:60–67. Figs. 5.

Touraine, A. *et al.* 1938. "Pili torti" familiaux (chez la mère et ses cinq enfants). *J. de Méd. de Paris* 58:401–403.

Toyama, Ichikawa & Hiraga. 1934. A previously undescribed anomaly of pigmentation. *Arch. of Derm. & Syph.* 29:433–434 (Abst.).

Trénel, M. & Prieux, M. 1930. Alopécie congénitale familiale héréditaire avec cataracte précoce. *Rev. Neurol.* ii. 561–565. Figs. 4.

Trotter, M. & Danforth, C. H. 1922. The incidence and heredity of facial hypertrichosis in white women. *Amer. Journ. Phys. Anthrop.*, 5:391–397.

Walker, A. E. & Bucy, P. C. 1934. Congenital dermal sinuses. *Brain* 57:401–421. Pls. 2, figs. 8.

Walker, R. 1936. Familienforschungen über die Zahnverhältnisse in drei urnerischen Tälern. *Arch. J. Klaus-Stift.* 11:571–600.

Weber, F. P. 1933. Psoriasis arthropathica in a woman whose twin sister was similarly affected. *Proc. Roy. Soc. Med.* 27:589–590.

Weber, F. P. & Lauber, H. K. 1939. Atypical psoriasis of axillae, with a remarkable family history of psoriasis. *Proc. Roy. Soc. Med.* 32:1583–1584.

Weech, A. A. 1929. Hereditary ectodermal dysplasia (congenital ectodermal defect). *Am. J. Dis. Child.* 37:766–790. Figs. 7.

Wehefritz, E. 1924. Zur Vererbung der Ichthyosis. *Zeits. f. Konst-lehre.* 10:394–400.

Weiner, A. L. & Levin, A. A. 1943. Pityriasis rubra pilaris of familial type. *Arch. of Derm. & Syph.* 48:288–296. Figs. 2.

Welch, H. 1917. Hairlessness and goiter in new-born domestic animals. *Univ. Montana Agric. Exp. Stn. Bull.* No. 119:83–104. Figs. 9.

Wende, G. W. 1902. Epidermolysis bullosa hereditaria. *J. Cutan. & Genito-Urin. Dis.* 20:537–547. Figs. 5.

Wende, G. W. & Bauckus, H. H. 1919. A hitherto undescribed pigmentation of the skin appearing in infancy in brother and sister. *J. of Cutan. Dis.* 37:685–701. Figs. 6.

Weninger, G. 1928. Sur les poils incarnés. *Ann. Derm. et Syph.* 9:687–694.

Weninger, M. 1933. Zur Vererbung des medianen Oberkiefer-Tremas. *Zeits. f. Morph. u. Anthrop.* 32:367–393. Fig. 1.

Wheelon, H. 1925. Clinical significance of the congenital absence of the upper lateral incisor teeth. *Endocrinology* 9:35–60. Figs. 6.

West, L. S. 1937. Observations on a family manifesting congenital ichthyosis. *Eugen. News* 22:77–85. Figs. 9.

Whyte, A. H. 1938. Post-anal so-called "pilonidal" sinus. *Proc. Roy. Soc. Med.* 31:982–984.

Wile, A. J. & Duemling, W. W. 1930. Familial xanthoma. *Arch. of Derm. & Syph.* 21:642–647.

Wilkey, W. D. & Stevenson, G. H. 1945. A family with inherited ectodermal dystrophy. *Can. Med. Assn. J.* 53:226–230. Figs. 4.

Wilson, A. G. 1905. Three cases of hereditary hyperkeratosis of the nail-bed. *Brit. J. Derm.* 17:13–14. Figs. 3.

Wilson, E. A. C. 1937. Hereditary sebaceous cysts. *Brit. Med. J.* ii. 185.

Wise, F. 1919. Multiple endothelioma of the skin. *Am. J. Med. Sci.* 157:236–253. Figs. 10.

Wise, F. & Satenstein, D. L. 1939. Epidermodysplasia verruciformis (Lewandowsky-Lutz). *Arch. of Derm. & Syph.* 40:742–754. Figs. 8.

Woo, T. L. 1942. The physical characters of the Pa Miao people of Kweichow and other peoples of South China. *J. Roy. Anthrop. Inst.* 72:45–53. Pl. 1.

Yaffe, S. A. 1942. Epidermolysis bullosa. *Can. Med. Assn. J.* 47:361–362.

Yamazaki, K. 1930. L'asymétrie mandibulaire et l'asymétrie de la dent de sagesse. *Bull. et Mém. Soc. d'Anthrop. de Paris* 1:12–16.

*Youle, H. 1858. A narrative of the Mission sent by the Governor-General of India to the court of Ava in 1855. London.

Zeisler, E. P. 1923. Pityriasis rubra pilaris — familial type. *Arch. of Derm. & Syph.* 7:195–208. Figs. 7.

Zeligs, M. 1932. Hereditary ectodermal dysplasia, anhidrotic type. *Am. J. Dis. Child.* 44:394–397. Figs. 2.

Zlotnikoff, M. 1945. A human mosaic. *J. Hered.* 36:162–168. Figs. 3.

Chapter XI

ANATOMICAL ABNORMALITIES OF THE HANDS, FEET AND LIMBS

ALMOST every conceivable and many unbelievable abnormalities of an anatomical nature are known to be inherited. Some of these are deficiencies of the skeletal development as a whole or of certain parts of it. Others refer to particular organs which may be absent or malformed. The classification of these abnormalities is a matter of some difficulty, as many of them refer to more than one organ system; some pertain to a single minor or even minute point of structure and others to a whole organ system.

Probably more abnormalities are known of the hands than of any other part of the body except the eye. There are also certain inherited differences in shape and structure of the hands and feet which are in no sense abnormalities. Not infrequently the little toe has only two phalanges, like the thumb and big toe. Pfitzner (1890) found that in 38 of 41 cadavers examined the little toes were bilaterally symmetrical, having three joints in 24 but only two in 14. Of 111 feet examined, 36 per cent showed the defect, 31 per cent of cases in males and 41.5 per cent in females. This condition was formerly ascribed to wearing tight shoes, but Elliot Smith has since found the same condition in Egyptian mummies where shoes were not worn.

Bagg (1929) discussed at length the origin and inheritance of foot abnormalities such as clubfoot, syndactyly, hypodactyly and amputation in the descendants of X-rayed mice.

Split hand and foot or "lobster claw" is a well-known and relatively rare abnormality often recorded in the white, black and yellow races. It may occur in the hands or feet or both.

Tubby (1894) records an early family in which the condition of lobster claw in the feet and partial suppression of the fingers was strictly dominant, 15 cases (10 ♂ 5 ♀) in four generations. Frequently there was one finger or toe instead of two, and one woman had only the feet affected. It has also been described in a father and two children in Annam. Stiles and Pickard (1943) describe another family in which the feet were more affected than the hands. There were 15 cases (11 ♂ 4 ♀) in four generations, strictly dominant. As the parents and grandparents of the original case were normal, he was evidently a mutation.

Roth (1911–12) quotes from Hartsinck, who wrote in 1770, the following reference to Negroes with "crab-claw" in Guiana.

> "Regarding the 'Touvingas,' or two-fingered negroes, it is observed that they are a people who had only two large fingers on their hands and two large toes on their feet, similar to those of a crab, as is figured in the illustration. The wrist is somewhat larger than that of the average man: the thumb and little finger are more than twice the usual size, and stand out from the limb, have a bend at the tip, and appear as one piece of flesh on which there is something like a nail. The palm of the hand has no bends, but appears as a solid mass, yet the divisions can be felt. . . . After the declaration of freedom, these negroes of Saramacca walked publicly through Paramaribo. . . . Many argue that they are not a distinct tribe or nation, but just a family who by accident or freak of nature have been thus deformed. These people are becoming very rare indeed, probably through intercourse with others, fast bastardising."

This represents an independent origin of the condition in Negro slaves. Their numbers are unfortunately not stated, but must have been considerable if they were regarded as an independent "tribe" or "nation." As the condition is dominant it would not disappear through crossing with normals.

Lewis and Embleton (1908) considered a collection of 180 cases of this deformity. Many varieties of the condition occur. In the "G" family, to which many of their data refer, the hands are variously misshapen, and each foot consists of two toes separated by a deep cleft. Rarely the toe on one side may be double, and the toes are generally bent claw-wise at their extremities. Both the hands and feet of these people are said to have great functional capacity and accuracy in use, including needlework and handwriting. Rarely one or both hands may be normal when the feet are split. The condition may also be associated with syndactyly (fused fingers) or polydactyly (extra fingers or toes). Cross bones frequently occur in the hands, but never in the feet. The inheritance is essentially that of a Mendelian dominant, though the expected ratios are not always adhered to.

In the "G" family there were forty-four deformed members in five generations. It never skips a generation, and derived normals × normals give only normal offspring. It is transmitted equally through either sex, sibships numbering 44 affected : 32 normal. Lewis and Embleton agree that it has arisen as a "sport" or mutation of germinal origin. They state "there are records of over thirty instances of the origin of this same sport," and account for this by the now generally accepted view that mutations tend to occur and recur. Since the character is dominant it cannot remain hidden in the germplasm, but must appear externally if the germ cell containing it develops into an individual.

All writers agree that this character segregates sharply, but Lewis and Embleton claimed that it "does not follow the laws of Mendel," because of the excess of abnormals in the offspring of crosses with normals. There is always a tendency, however, for the normals not to be fully ascertained. Lewis and Embleton believe there is a "decided tendency for the deformity to die out" in later generations. They appear to think that this results from the germinal condition representing split-foot becoming unstable. Probably the struggle for existence and sexual selection are sufficient to account for this.

Three cases in which the left hand only is split are described by Hanhart (1945) in a family. Father and son were affected, and a distant cousin with a common pair of ancestors five generations back. This appears to be a dominant of very low penetrance, affecting especially digit III; with possibly an inhibiting gene in the family, as some other members show a slight expression in the fingers.

A family with 5 cases of *monodactyly* (1 ♂ 4 ♀) in three generations is cited in *Lancet* i. 743 (1908). The little finger was present, but four fingers and their metacarpal bones were wanting. The feet were similar but some showed lobster claw, to which the condition is closely related, inheritance dominant.

Pearson (1908) referred to the existence in Scotland of a family, "the Cleppie Bells," with a deformed hand inheritance extending over two centuries. He traced the deformity in another family for four generations, and found again an excess of abnormals in the offspring of crosses with normals (25 : 14). The stock of this family is otherwise normal, and they have no difficulty in finding normal mates. The gait is ungainly, but the children at school hold their own in writing, drawing and needlework. Additional data for this family are given by McMullen and Pearson (1913), the numbers of abnormals recorded having increased from twenty-five to thirty-three. In the third generation the result is in conformity with the Mendelian expectation of equality of normals and abnormals. In the fourth and fifth generations there is a total of 28 affected : 13 normal.

This condition is evidently due to a single dominant factor which arises from time to time as a mutation. Lewis (1909a) records certain other split-foot pedigrees. These include (1) a family of ten, in which half are abnormal and half normal; (2) a family of six, all abnormal. In the latter the father may perhaps have been homozygous.

Yap and Pineda (1922) record two cases of *ectrodactyly* (absence of digits) and syndactyly in unrelated Filipino women. Both hands and feet were affected and neither woman had any affected relative. Klein (1932) described two brothers who agreed in having a normal thumb and little finger on each hand, with a single digit between, only the distal segment of which appeared normal, and slight webbing between toes II and III. The parents were uncle and niece and there were no deformities in the previous three generations, a sister also being normal, so the gene was evidently recessive in this family.

In lobster claw, certain bones are misplaced, as in clubfoot, but other bones or digits may be missing altogether. The same is true of certain muscles, showing that individual bones and muscles may behave as units in embryological development.

Modern experimental embryology has shown that excised embryonic bones cultivated *in vitro* take their peculiar shapes mainly owing to intrinsic factors. Fell and Robison (1929) isolated the femora of a six-day chick embryo in a watch-glass with culture solution and found that they increased to more than three times the original length and underwent a remarkably normal histological differentiation. Small-celled epiphyses, periosteal bone and membrane were formed and the characteristic terminal processes, condyles, head and trochanter were all developed. The isolated embryonic bone synthesized a phosphatase which was not present in the explant. This enzyme was formed by cartilage and disappeared when the cartilage was transformed into bone. Murray (1926) seems to have been the first to show on an extensive scale the self-differentiation of limb bones of the chick. Fell (1934) excised the region of the embryo knee-joint and showed that from a block of mesoderm the two opposing articular surfaces develop through intrinsic factors *in vitro;* but in explants the joint eventually disappears by secondary fusion.

The brain of a living young rat proves to be a favorable medium, in which embryonic bones and other structures will grow and differentiate, the host rat being rarely affected. Willis (1935) found that cartilage, bone, bone-marrow, epidermis, epithelia, teeth, salivary gland tissue and skeletal muscle would grow and differentiate in these conditions at almost the normal rate. Later (Willis, 1936) the undifferentiated cartilaginous primordia of the long bones from rat embryos, implanted in the brain of a rat, were found to grow at normal rates into fully formed long bones. Glasstone (1938) showed similarly that the teeth are self-differentiating. Molars of rats and rabbit embryos explanted to tissue culture before the cusps appeared were found to develop cusps which were almost normal in shape, number and arrangement, with the formation of odontoblasts, dentine and enamel. Fell (1940) has recently summarized this subject, referring to much other significant work in this field.

Popenoe (1937) points out that the marginal rather than the central digits may be suppressed and the latter fused into one. The defect in one member may be slight, such as lack of nails. He cites the case of a boy with normal parents, whose right hand has a thumb and finger with metacarpals and phalanges while the other three digits and their metacarpals are suppressed. X rays showed that there was no ossification centre for the carpus and no epiphyses were visible on the radius or ulna. The left hand showed a single central digit with three phalanges and a metacarpal, the wrist being in the same condition as in the right hand. This was probably a mutation, as it is unknown in the ancestors. It might possibly, however, be a recessive outcrop. While usually dominant, Fetscher (1922a) found two cases in the second and third generations of a family with a common pair of ancestors. This gene was either recessive or possibly a dominant of extremely low penetrance. Liebenam (1938b) reports a family with dominant split-hand and split-foot, 14 cases (11 ♂ 3 ♀) in five generations. In one affected individual one hand and in another both hands were normal.

Pearson (1931) recorded the presence of "lobster claw" in chimpanzees and in rhesus monkeys. The conditions are exactly the same as in man and may also be combined with syndactyly. No doubt these parallel mutations are inherited, as in man.

Clubfoot, on the other hand, is generally recessive, or possibly in some families a dominant of very low penetrance. Purely dominant pedigrees also occur, but they appear to be less frequent. Fetscher's (1922b) thirty-two pedigrees contain only six cases of direct transmission from parent to child, and in some at least of these the other parent may be heterozygous. It is curious that these two related anomalies should be so different in their inheritance. The frequency of clubfoot is estimated at 1 in 1000–1600. From a study of 186 cases in 25 families, Fetscher finds, in conformity with earlier ratios, that the sex-ratio of affected individuals is 67 ♂ : 33 ♀ or 2 : 1. He finds that in clubfoot (pes varus congenitus) × normal, 11 per cent of children have clubfoot, whereas with a single factor and no other disturbances the expectation would be 50 per cent. Similarly in normal × normal from clubfooted parents, 5.3 per cent of children (not 25 per cent) were affected. This may be regarded as low penetrance. Fetscher concluded that half to three-quarters of the cases of clubfoot are heritable, due to a nervous derangement, and that the other cases have no single cause, but may result from bone defects, uterine anomalies or from multiple births. He developed an improbable theory based on non-disjunction of chromosomes, to account for the inheritance. In the various pedigrees are numerous associated defects, including microcephaly, dwarfism, Mongolism, deaf-mutes, cleft-palate, idiocy, epilepsy, hysteria and suicide.

Müller (1926), in an important study with an extensive bibliography, points out that it was recognized a century ago that clubfoot resulted from spastic muscular contraction, the bones being drawn out of their proper positions. Since then two explanations of its pathogenesis have been discussed: (1) a germinal defect; (2) external pressure on the normal foot. Most recently clubfoot has been viewed as a neurogenic or myogenic deformity, caused by malformation of the caudal end of the spinal cord, or dystrophy of the leg muscles, of purely peripheral origin. It is clear that a series of conditions of very different etiology and anatomical structure are included under the term *clubfoot.* Müller examined 358 cases. Delay in ossification of the tarsal bones is a factor in congenital cases which relapse after treatment.

The condition is classified as of three types: (1) pes varo-supinatus, 61 per cent; (2) pes varo-excavatus, 24.8 per cent; (3) pes varus, 14.2 per cent. He circulated a questionnaire regarding inheritance and got replies from 262. It is clear from the results that, like so many human abnormalities, the methods of inheritance are various, as shown by the 40 pedigrees, in which there are many irregularities and frequent skipping of a generation. The following types occur: (1) unilateral clubfoot, inherited always on the same side or changing between right and left; (2) symmetrical, always in both feet; (3) changing between unilateral and symmetrical (four pedigrees). One pedigree shows dominant clubfoot bilateral through four generations. Dominance occurs probably in nine of the pedigrees, in twenty-nine there is no dominance. The dominant pedigrees are all pedes varo-excavati, two of them unilateral, seven bilateral. Among the apparently recessive pedigrees, both varo-supinati and varo-excavati occur (the latter only in six pedigrees). In one family the eldest son had clubfoot at birth, while others developed it during childhood. The appearance of clubfoot after birth is rare (1 per cent) in supinati, but common (23.5 per cent) in excavati. In two pairs of apparently identical twins, one had bilateral clubfoot, the other was normal. This probably represents a type with low penetrance.

The various types of clubfoot (talipes) are frequently named after the part walked on. Thus in t. equinus the toes are walked on owing to elevation of the heel by contraction of the tendon of Achilles. In t. calcaneus the toes are elevated and the heel walked on. In t. varus the outer border of the foot is used, in t. valgus the inner border.

Various combinations of these also occur. In t. cavus the foot is highly arched. All forms of talipes are due to irregular development of the tissues of the foot, the bones retaining their normal shape but being pulled into different positions by the muscles, while ligaments may be deficient or absent.

In very young children the clubfeet are almost invariably supinated, and this can change during development to varo-excavatus. The percentage of inheritance of varo-excavati is twice that of supinati, and they show a normal sex-ratio. Twenty per cent of all cases of clubfoot, or 15 per cent of congenital clubfoot, Müller concludes is of the recessive type — not a simple recessive, but either involving polymery or due to an inherited disposition to clubfoot being suppressed by paratypic conditions. The latter alternative, now called *failure of penetrance*, is the more probable. The largest group is that in which neither heredity nor abnormal intra-uterine conditions can at present be shown. In the undoubtedly inherited cases the sex-ratio of clubfooted is 2♂ : 1♀, and as the doubtful group above mentioned has the same ratio they probably also come in the inherited class. Spina bifida appears frequently with clubfoot.

That misshapen feet and other abnormalities can result from mechanical pressure within the uterus before birth has been convincingly shown by Browne (1936), but such cases are few compared with those due to heredity.

Isigkeit suggested that the gene for clubfoot is recessive sex-linked, but Debrunner (1940) found one case of direct transmission from mother to daughter and another from father to son, although a generation is very frequently skipped. The statistical relations are not in accord with a dihybrid recessive sex-linked heredity. Debrunner comes to the conclusion, after study of 140 cases, that congenital clubfoot is a monohybrid recessive, but suggests that it probably requires for its expression a "realization-factor" as well. His statistics combined with those of Isigkeit and Fetscher give a ratio of 58.6 per cent affected males to 41.4 per cent affected females, but Debrunner collected from the literature 6872 cases of clubfoot and the sex-ratio was 66.2♂ : 33.8♀. Possibly the Y-sperm bearing the gene for clubfoot on an autosome is more viable than the X-sperm bearing this factor. But in clubfoot families there appears to be an excess of *normal* males also (111♂ 81♀), so the explanation of this 2 : 1 ratio can only be reached after statistical enquiry on a larger scale. The inheritance of clubfoot has also been investigated by Scherb (1939), who concluded that several different genes produce it. He regards clubfoot in the strict sense as combined with spina bifida and neurogenic in origin, showing muscular paralysis or hammertoe; but clubfoot also occurs without spina bifida. DeLucchi's (1938) family had 8 cases (3 ♂ 5 ♀) in four generations, the inheritance dominant. He found clubfoot associated with luxation of the femur in several published families. Martmer (1927) described a mother and two children with *talipomanus* or clubhands.

Studer (1944) describes a man of 45 with an extreme form of bilateral clubfoot (talipes varus). The ulna of the right arm was also defective and digits IV and V were lacking in both hands and V in the left foot. Clubfoot was combined with syndactyly, ectrodactyly and brachymesophalangy. Dissection of the arms and feet showed muscular atrophy and anatomical abnormalities of muscles and nerves, including enlargement of the tibial nerve. The condition was regarded as endogenous in origin.

Brachydactyly

This was the first case of Mendelian inheritance demonstrated in man. Farabee (1905) showed in a family in Pennsylvania, that it is inherited strictly as a simple dominant. Matings of brachydactyl with normal gave 50 per cent of each type (36 affected : 33 normal).

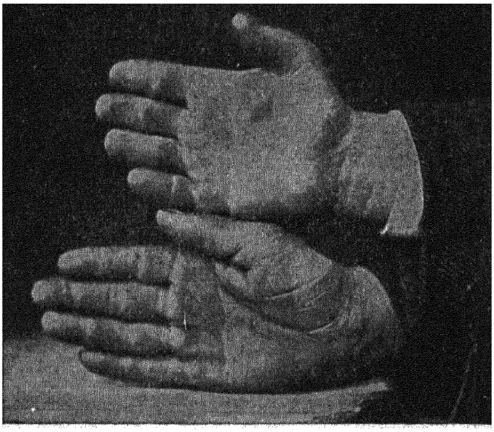


Fig. 133. Brachydactylous and normal hand. (After Drinkwater)

Although much less frequent than split-foot or clubfoot, the inheritance of various forms of brachydactyly has been more studied in recent years. Figure 133 shows the condition, in comparison with a normal hand, and Fig. 134 shows the presence of only two phalanges in each finger. Brachydactylous women cannot play the piano well owing to their inability to span the octave. Brachydactylous men in this family include farmers, mechanics, business men and school teachers. One was head of a commercial school and a fine penman, another was a baseball catcher. The arms and legs are short, but the sitting-height is nearly normal, and abnormals are stouter than their normal sibs. There is an unverified tradition in the family that the first member with short fingers came from Normandy in the army of William the Conqueror. Brachydactylous individuals have never intermarried; but the abnormals always marry first, and will soon have gained a generation in this way.

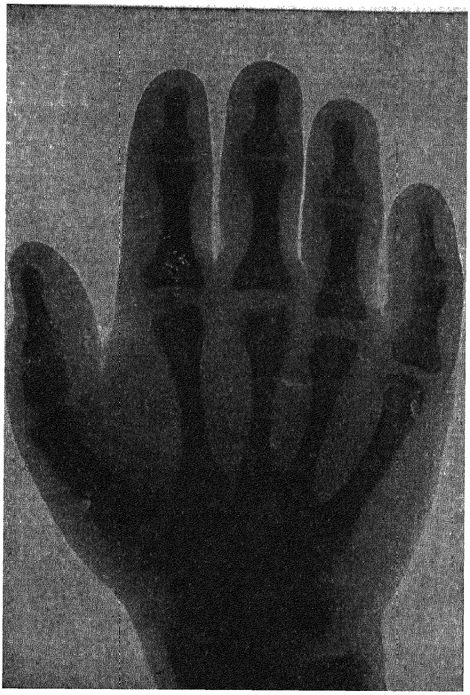


Fig. 134. Skiagraph of a brachydactyl hand, showing two phalanges in each finger. (After Drinkwater)

Drinkwater (1908) independently investigated a British family, with the same results as regards inheritance. He found that the strength of grip in brachydactylous individuals was considerably below the average. They complain that they cannot play the piano or any other musical instrument requiring normal length of fingers, their grasp of objects is smaller than normal, and the women cannot do netting. That they are handicapped is shown by the fact that their social position is lower than that of their normal relatives. They are engaged in unskilled labor, while their normal relatives include farmers, grocers, etc. In a wild tribe where personal defence with weapons is a necessity, brachydactylous individuals would probably not survive.

In several papers Drinkwater made a careful anatomical investigation of brachydactylous hands and feet, including radiographic studies. The condition applies equally to fingers and toes, and is accompanied by short stature. In the digits he showed that the middle phalanx is very short, and has become ankylosed to the base of the terminal phalanx. Hence the second phalanx is rudimentary, and at a certain stage of development it unites with the terminal phalanx. The most important feature is the absence of the epiphysis (terminal cartilage, which becomes ossified) at the base of the second phalanx. The epiphysis may also, perhaps, be missing in some cases from the third phalanx, the second and third phalanges consisting of a single piece of cartilage. The metacarpal (hand) bones are also more or less abnormal, but the metatarsal (instep) bones are unaffected. Defective epiphyses of the long bones probably accounts for the shorter stature.

This abnormal family was very prolific, the number of children in nine families averaging eleven each. A normal woman had forty-five descendants, while a brachydactylous woman in the same family had ninety-nine descendants. The numbers in successive generations show that the condition is on the increase, and that there is no chance of it becoming extinct so long as the brachydactylous members continue to marry. For some unknown reason they do marry more frequently and earlier than their normal sisters.

The essential feature in brachydactyly is the absence of the epiphysis at the base of the second phalanx, with subsequent ankylosis of the second and third phalanges. The fingers are about half the normal length. Although brachydactylous individuals are lacking in some forms of dexterity, and therefore must accept a lower social status, yet they show a decided increase in fecundity compared with normal members of the same family. In this family, twenty-five now living in England and Wales are brachydactylous. Beginning with the fourth generation, the total number of descendants from DR × RR crosses is 75, of whom 39 are abnormal.

No connection could be traced between Drinkwater's first brachydactylous family and the one described by Farabee, there being no surname common to the two families. Drinkwater (1915) has since described another family, however, which he has shown to be descended from a member of Farabee's family, who removed from America and settled in England. In this family and its American antecedents the abnormality can be traced for six generations. In both of its branches the proportion of females among the abnormals is exactly 61 per cent. In the English branch 50 abnormals were recorded to 48 normals, showing that heterozygous brachydactyls produce the two types of germ cells in equal numbers. Normals mated together invariably have only normal offspring. The shortness of stature of brachydactyls is shown to be due to the short legs, both femur and tibia being shorter than in normal members of the family. Iltis (1944) describes a small family with four cases (♀) of this rare abnormality in four generations.

Drinkwater has also described in two families the condition which he calls *minor brachydactyly* (1912, 1914). In a Lancashire family this abnormality has been traced through five generations, and sixteen abnormals were living when the study was made. The fingers are less shortened than in brachydactyly, but the middle phalanx of each finger is abnormally short. This is partly due to the absence of the epiphysis from the base of the second phalanx, except in the middle finger, and also to a slight shortening of the second phalanx, but is chiefly due to the fact that the cartilage between the shaft and the epiphysis becomes prematurely ossified, thus causing cessation of growth in length of the fingers at an early age. Union of the epiphysis with the second phalanx frequently occurs earlier in the first and fourth fingers than in the second and third, thus leading to a greater shortening of the former. The abnormality of the toes is practically identical with that in ordinary brachydactyly. This family is also shorter in stature. As in the brachydactylous family, the women are 4¾ in. and the men 8 in. shorter than their normal siblings. A total of 21 abnormals : 26 normals was recorded in families having one abnormal parent. The abnormals in this family are said to have better health than the normals. In the children the abnormality is inconspicuous, and is sometimes detected only by flexing the finger.

In the second family showing minor-brachydactyly (Drinkwater, 1914), the conditions closely resemble those in the previous family, but so far as the records go back there is no connection. It is found in five generations, there being nine abnormals to ten normals, eight of the former now living. They are all descended from an illegitimate daughter of a short-fingered man, the mother having been married to a normal man by whom she had entirely normal descendants. These forms of brachydactyly are, therefore, all simple Mendelian dominants. They show a clear tendency to increase rather than die out, notwithstanding their social handicap, or possibly on account of it.

Lewis (1909b), in a thesaurus of the work on brachydactyly up to the time his paper appeared, cites two other cases with interesting features. In Mercier's case a French family is described in which eighteen members in three generations are brachydactyl, having two phalanges on all the fingers and toes. In Hasselwander's case (a German family) there were six abnormal members of the family in three generations. The original brachydactyl of this pedigree came from normal parents and probably marks an independent origin of the condition through mutation. The actual origin of such a case is naturally difficult to prove, and this can only be done where the conditions in both parents and grandparents are accurately and certainly known to be normal.

That various other modifications of typical brachydactyly, in addition to those described above, are inherited in the same way is shown by such records as those since published by Drinkwater (1916). He traces through four generations a case of *abnormal segmentation* of the index and middle fingers, the third finger being much longer than any of the others owing to the great length of its proximal phalanx. The first and second fingers are also more or less tilted away from the thumb (see Figs. 135, 136). The sibships in this family number 15 affected : 21 normal. The feet show ordinary brachydactyly. From a careful study of skiagraphs the following anatomical interpretation emerges: The index finger has at its base an extra triangular bone which sets the finger obliquely to the hand. The proximal phalanx of the middle finger appears to be divided equally or unequally into two parts; the lower part, however, is probably an extra bone corresponding to that in the index finger, and it also is set somewhat obliquely. In the adult hand these extra bones become ossified with the proximal phalanx of the ring finger. All these anatomical features behave as a unit in inheritance, with remarkably little variation in their development.

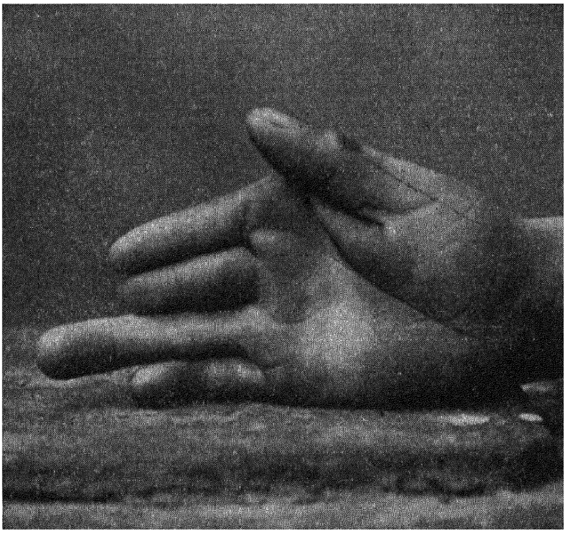


Fig. 135. Hand showing abnormal segmentation of index and middle fingers. (After Drinkwater)

Greene and Saxton (1939) described skeletal abnormalities in the rabbit, ranging from brachydactyly to acheiropodia. The condition was determined by one *recessive* factor which produced a series of conditions from slight digital shortening to absence of hands and feet. The extent and location of the abnormalities was controlled by two groups of genes which behaved as quantitative modifying factors. Embryologically, the first abnormal change was dilatation of the blood vessels in the affected limb buds, followed by hemorrhage and necrosis and in some cases sloughing of the affected parts.

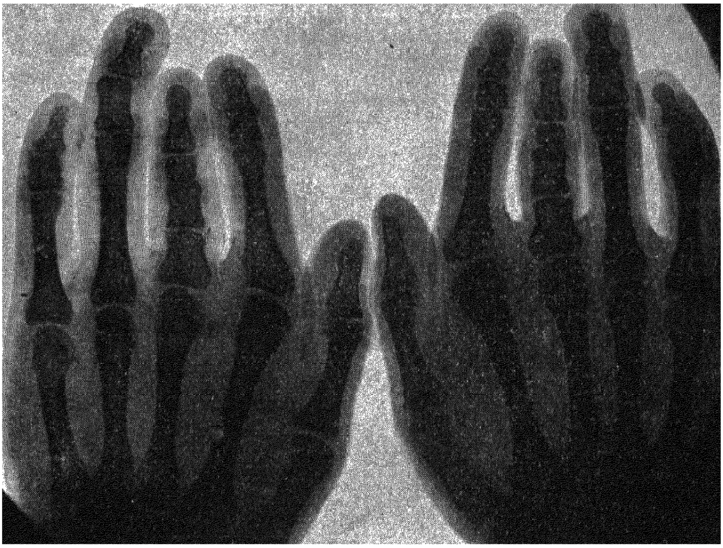


Fig. 136. Skiagraph of the hands of a girl aged 19, in the same family as Fig. 135. (After Drinkwater)

Drinkwater (1917) has described yet another digital abnormality closely related to brachydactyly, which is remarkable for the number of generations for which it is known to have been handed down in one family. It is now called *symphalangism.* The peculiarity is as follows, as found in the hands of a gentleman, A. T., of the present generation. In the middle finger the joint between the middle and basal phalanges is only very slightly movable, the articular surfaces of the bones being enlarged, while in the ring and little fingers there is no joint between the proximal and middle phalanges, these two being completely fused into one (see Fig. 137). All the fingers are movable at the distal joint, and both hands are alike. All the toes, except the hallux, are affected exactly like the ring and little fingers. This man's father and *his* mother are known to have had precisely the same abnormality. His father married twice, and one of the half-brothers shows it. The most interesting feature of this case is that A. T. is a direct descendant in the male line from John Talbot, the first Earl of Shrewsbury, who figures in Shakespeare's *Henry VI,* and was killed in battle near Bordeaux in 1453. Tradition has it that his thigh bone was broken while on horseback, and that when he fell from his horse he was killed by the blow of a battleaxe on the head. His body was buried in a tomb inside the church at Whitchurch, which was surmounted by a stone effigy. In 1874 the tomb was opened and repaired by one of his descendants. The skeleton was identified by the cleft skull and the fracture of the right thigh bone. The finger bones, when examined, showed the same ankylosis that exists in his modern descendant. On the stone effigy the fingers, which were somewhat damaged, also showed precisely the same thickening of the middle joint as described in his descendant. Clearly, then, this defect has been handed down for more than five hundred years as a Mendelian dominant, and the genealogy of the family shows that it must have been inherited through fourteen generations. This is one of the longest periods on record for the tracing of an anatomical abnormality in man, though the Hapsburg jaw extends back equally far.

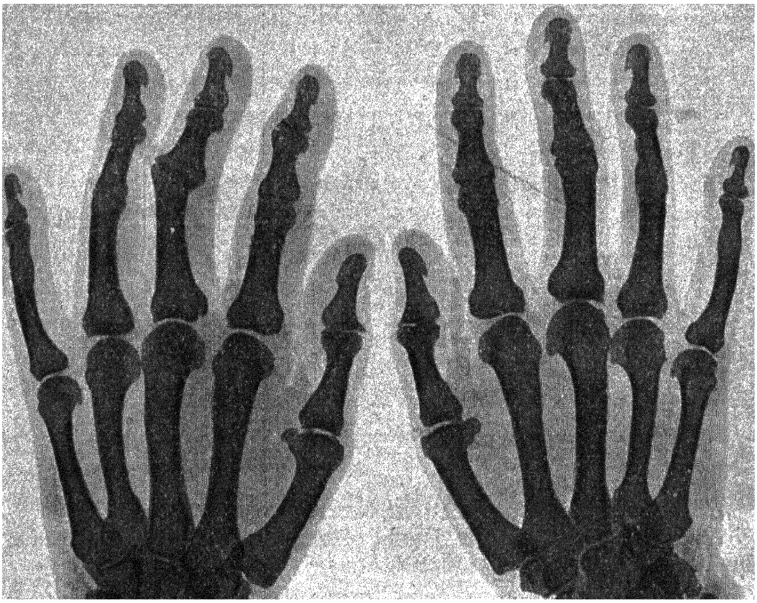


Fig. 137. Skiagraph of the hands of A. T., showing the absence of a joint between the proximal and middle phalanges of the ring and little fingers. (After Drinkwater)

Walker (1901) described a family in Maryland, with ten cases in five generations, of a condition very similar to the above. In digits III and IV the joint between the proximal and middle phalanges is missing and in addition the terminal phalanges are often absent from digits IV and V (hypophalangy). Congenital *ankylosis of the terminal joint in* *the index finger* only (Cole, 1935) occurred in 9 members (2♂ 7♀) in five generations. The terminal and middle phalanges on some of the toes were also fused. This is probably a dominant with low penetrance. There are at least four previous reports of a similar kind. Another case of symphalangy or orthodactyly was described by Daniel (1936) in a Welsh family of Scottish ancestry, with 16 cases (6♂ 10♀) in five generations. It is strictly dominant and the sibships number 14 affected : 14 normal. The terminal joint of the index fingers was inflexible due to fusion of the phalanges. The mid-phalanges were abnormally short and in certain cases other finger joints were affected and finger-nails were absent. The name suggested is *phalangeal anarthrosis* of the index finger.

In the United States, Cushing (1916) has described essentially the same condition, but no connection with the English family can be traced. Those who have it are commonly spoken of as *straight-fingered,* because the fingers can only be partly closed on the palm. The terminal joints can be flexed, although the rest of the finger is straight. The greater effect on the middle phalanges is true also of Drinkwater's minor-brachydactyly, and is probably due to the fact that the ossification centres appear later in this phalangeal row, this being the last row, and the terminal row the first, to ossify. The toes are likewise affected, even occasionally (as in "lobster claw") when the hands appear normal.

It is quite probable, according to Cushing, that the articulations between the proximal and middle rows of phalanges are the last to be laid down, and that "an inhibitory influence checks their development at a stage a few days later than that which checks the formation of the ossification centres and produces brachydactyly." Hence both are conditions of arrested development in different degree. According to Cushing, long slender fingers (arachnodactyly) may result from deficiency of pituitary secretion, while excessive secretion produces short, stubby fingers.

The original member of this "straight-fingered" family, William B., migrated from Scotland to Virginia in 1700. He married, and from him are descended seven generations, most of whom still live in the same region of Virginia. A member of the fifth generation has communicated with a Scottish relative who shows the trait. The inheritance is dominant, the family including 452 individuals in eight generations. Of the 150 children of an affected parent in twenty-eight completed families, seventy-eight of them, or 52 per cent, carried the trait. There is considerable variation in the expression of the character, and it may be transmitted in extreme form by a parent who appears to be but slightly affected. In one case a woman who was doubtfully abnormal, but transmitted the trait, was shown by skiagraphs to have the condition only on the little finger of one hand.

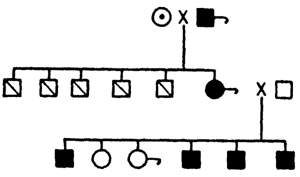
Another family with the same peculiarity of fingers, which cannot be flexed properly, is described by Duncan (1917). It is perhaps related to Cushing's family, since its ancestors are said also to have come from Scotland. The second joints of the fingers, and frequently also of the toes, are perfectly inflexible. The character is dominant in four generations, the original affected parent (male) being heterozygous.

Rochlin (1928) cites from the literature several other cases of the inheritance of *stiff fingers* with ankylosed proximal finger joints, and describes a family with seven cases in four generations. Typically the middle joints of digits II to V on both hands were affected, as shown by skiagraphs; but there were variations, and the toes might also be affected. This condition is also dominant and presumably arose as a mutation. Wilmoth (1930) cites a family in which the proximal phalangeal joints on the four fingers of both hands were fused. The ring finger on each hand also lacked a distal phalangeal joint and the terminal phalanx of each little finger was flexed at 90°. The tarsal-metatarsal joints were fused except on each big toe, and the terminal phalangeal joint of the second toe of each foot was also ankylosed. The condition was dominant, with six cases in three generations.

Symphalangy has been described (Hefner, 1924a) in a family from Ohio, dating back to the American revolution and showing a dominant inheritance with twenty-three cases in six generations. The original ancestor, Joseph B., and his wife emigrated from Virginia, whence Walker's family also emanated. Cushing believes that Joseph B. is a grandson of the William B. in his pedigree, and thus these two pedigrees are connected. Probably also Walker's family belongs to the same stock, and possibly all trace back to the Earl of Shrewsbury's line, so that the mutation would have happened but once. In Hefner's pedigree, the sibs from DR × RR matings number 22 with fused joints: 27 normal. The ankylosis shows some variation; all four fingers may be affected or only the little finger, and in one individual the condition was only present on one hand. Affected persons were flat-footed, but the toes were normal. Inman (1924) briefly describes another family from Ohio with four cases in four generations of direct descent. In the case examined, the fingers were not shortened and the symphalangy occurred in digits II and V of both hands, also in digits II–V of both feet. Freud and Slobody (1943) describe an Indian-Negro family with five cases of dominant symphalangy in four generations, one joint being suppressed.

Another pedigree of a short-fingered family is given by Mohr and Wriedt (1919), who review the literature of brachydactyly. The case they describe, with numerous photographs and skiagraphs, is of a Norwegian family, some of whose members migrated to North America. The malformation consists in a shortening of the second phalanx of the second fingers and toes only, and is called *brachyphalangy*. There is no shortening of the stature. The condition occurs in two degrees: (1) so slight as to be often overlooked or even invisible. This condition may really be widespread in the population. (2) More extreme, probably due to the presence of a modifying or intensifying factor. The inheritance is that of a simple dominant. It has been traced through five generations of descendants from a brachyphalangous woman born in Norway in 1764, with 32 cases (15♂ 17♀). Detailed knowledge of the earlier generations is obtained from a carefully kept "family book." In two lines descended from an affected daughter and an affected son of this woman, every individual is recorded. In one case intermarriage within affected lines apparently produced an individual homozygous for the character. She was a cripple without fingers or toes, and died at the age of one year. This shows how serious even a slight abnormality may become if present in the homozygous condition. It corresponds with many of the lethal factors known in *Drosophila* and other animals. The writers refer to Mackinder's (1857) record of a family, in which brachyphalangy combined with hypophalangy (less than three phalanges) was transmitted as a dominant for six generations. This was in 1857, before even Mendel's original work was done.

Wegelin (1917) traced through three generations an abnormality producing *crooked little fingers*. The terminal phalanx is bent to the radial side, the middle phalanx shortened, and its distal end oblique. It is dominant, but there were fourteen abnormal to two normal in the third generation. Macklin (1927) gives a pedigree (Fig. 138) of a crooked little finger and color-blindness. The grandparents were cousins and the grandmother must have been a carrier for color-blindness, as the daughter, II. 6, was color blind. She must have been homozygous for the condition, as she transmitted it to all four of her sons. The crooked little finger is independently inherited as a simple dominant. Thomas (1926) recorded a pedigree with 7 cases (6♂ 1♀) in three generations in which a bent and stiff little finger on the right hand was inherited



▧ = Died in infancy

Fig. 138. Pedigree of color-blindness and a crooked little finger. (After Macklin)

as a strict dominant. Stiles and Schalck (1945) cite a family with *curved fore-fingers.* The two distal phalanges are deviated to the ulnar side. A single dominant gene is indicated. The family examined showed 34 cases (14 ♂ 20 ♀) in four generations, generally bilateral. X-rays show that the bones are normal. This condition is less marked than clinodactyly and is not an abnormality. The little fingers are also usually slightly crooked, sometimes even digits III and IV. This aberration is fairly common and may be genetically useful. In a family in North Carolina (Murphy, 1926) there were 33 cases (21 ♂ 12 ♀) in five generations of *finger contracture,* bilateral, most marked in the little fingers, and probably due to shortening of the joint capsules. This dominant condition was congenital, more frequent in males than females, and often (11 cases) associated with subluxation of the knee-joint as well as other defects, mainly skeletal.

The remarkable accuracy of the inheritance of many digital malformations is shown incidentally by a paternity case (Mohr, 1921), in which the alleged father had a pronounced brachyphalangy affecting the second row of phalanges on fingers and toes II, III, and IV. The thumbs were normal, but the basal phalanx of the great toe was shortened. The hands and feet of the child showed exactly the same malformation, and skiagraphs indicated absolute correspondence in the bones. The man was therefore adjudged to be the father.

In another case (Rieder, 1889) the father had a rudimentary (short) fourth metacarpal bone, the ring finger being also short and small. The daughter exhibited "lobster claw" in the right hand, while the feet showed absence of certain toes, reduction of certain phalanges, and syndactyly. Such combined abnormalities in a line of descent are not infrequent.

Hall (1928) contributes two pedigrees from the mountains of northwestern Shansi, China. In the Ch'en family there is complete *ankylosis of the proximal joint* in the fingers and toes. This generally involves digits II–V, but the thumbs and big toes are not affected, nor is the length of the fingers. The distal joint shows more movement than usual. There were 47 cases(28 ♂ 19 ♀) in seven generations, the condition being strictly dominant, with no skips, sibships 39 normal: 46 affected. The excess of affected is quite possibly due to fuller ascertainment. The proband stated that of 300 known members of his family at least 100 were similarly affected. An independent family showed a similar condition. In the Ho family there was a shortening of the middle phalanx, especially in digits II and III, which made the middle finger very short. The middle finger also had an extra small basal phalanx (perhaps an enlarged epiphysis). This dominant condition was present in four cases in three generations.

Brachydactyly may occur in the hands only, the feet only, or in both, and the three conditions are more or less independent. Cutter and Nelson (1931) cite a family in Oregon in which only the toes are affected, having two joints. From the incomplete pedigree in three generations the condition is dominant, but a father in whose toes there were three abnormally short phalanges transmitted the condition.

Brachydactyly (short fingers) can occur either as brachyphalangy (shortening of phalanges) or as hypophalangy (absence of certain phalanges). Marshall's (1929) family is like Drinkwater's Liverpool family (1908). The mid-phalanx was not really absent, but early united with the terminal phalanx in Drinkwater's family. In Marshall's family, with seven cases in four generations, the mid-phalanx was rudimentary and not fused with the terminal phalanx. Nissen (1933) described a New Zealand family in which there is *shortening of the middle phalanges* of the fingers and the proximal phalanx of the thumb. There is also a variable degree of shortening in other phalanges and in the metacarpals, with frequent fusion between the middle and distal phalanges, the epiphyses being constantly absent from the middle phalanges. The feet show corresponding changes. Drinkwater pointed out that the absence of an epiphysis predisposes to fusion.

Retardation of the epiphysial union and retention of the epiphysis as a separate bone occurs normally in the sea mammals (seals, whales, walrus). In cases of Mongolism and myxoedema all the metacarpals may have proximal epiphyses — a condition which may represent an endocrine retardation of skeletal growth. Thus digital abnormalities may have both a phylogenetic and a physiological significance.

This form of finger-shortening is strictly dominant, the family having 32 cases (11 ♂ 21 ♀) in five generations (sibships 32 affected: 32 normal). The 2 : 1 ratio of affected females to males is unexplained. This family originally emigrated from Derby to Australia in 1840 and the New South Wales branch was described by Lipscomb (1915). He shows that digits II and V in both hands and feet have only two phalanges, the middle one being absent, while digits III and IV have three phalanges but the two distal ones are rudimentary in fingers and toes. The pedigree is strictly dominant, with 14 cases (6 ♂ 5 ♀ 3 unstated) in five generations, the sibships 13 affected : *ca.* 14 normal.

Walter (1938) described a large family of mountaineers in West Virginia with 39 cases (16 ♂ 23 ♀) of short digits in five generations. The dominance was strict. There are no anatomical details except that some had part or all of their fingers short, others had short toes and some had both.

That brachyphalangy and hexadactyly are not necessarily always dominant is shown (Gates, 1933) by the son of a second-cousin marriage, who had an extra little finger removed from each hand. The second and third phalanges in the fingers were very short, the nails very small or missing, and the little fingers strongly bent. The toes of the pentadactyl feet had similar abnormalities. The condition resembles brachyphalangy in that the fingers, toes and stature were affected (he was 4 ft. 7 in. high at twenty-four years of age, and stout), but the condition of the nails was like apical dystrophy. His ancestors for three generations were normal.

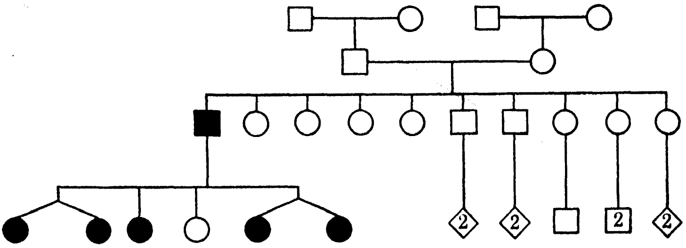


Fig. 139. A mutation showing a combination of brachyphalangy and hypophalangy. (After Liebenam)

A pedigree of Liebenam (1938) shows a combination of both methods of shortening the fingers. Case III. 1, from normal unrelated ancestors, appears to be a mutation (Fig. 139). He was the eldest of ten children, the others all normal, and there is no skeletal abnormality in his ancestry. Some fingers show two phalanges and some three short ones, but the nails are constantly large and the toes are like the fingers. Five of his six daughters, including two pairs of non-identical twins, are like their father. He was born with short, broad hands and feet and was small (153.4 cm. tall) but well proportioned. His paternal ancestors were tall and slim, but on the mother's side they were small and compact like III. 1. As brachydactyly is connected with short stature, it seems possible that the mother's family contributed some element to the production or expression of this dominant mutation. Perhaps her heredity combined with that of an exceptional germ cell from the father tipped the balance into a new condition more extreme than that of the mother alone.

In another family (Becker, 1939) the *middle phalanx* is short in fingers and toes (*brachymesophalangy*). There were 15 cases (8 ♂ 7 ♀) in five generations, dominant with one skip, the sibships numbering 15 affected to 16 normal. The fingers show considerable variation, including hyperphalangy (four joints instead of three), clinodactyly, camptodactyly and shortening or decrease in size of single metacarpal or carpal bones.

Danforth (1919a) described a condition which he called *brachydactyly* in fowls. Such birds differ from the normal in that digit IV, instead of having five phalanges and being longer than digit II, varies from as long as II (not longer) to a toe having only two phalanges and no nail. He treated with alcohol (1919b) fowls which were heterozygous for brachydactyly, polydactyly (extra toes), and white color — both males and females, the alcohol being inhaled for short periods. A larger percentage of brachydactylous birds was consistently obtained in the offspring of treated males, indicating that germ cells carrying brachydactyly were more resistant than normal germ cells. This experimental method should be applicable to a variety of cases, and furnish evidence of the relative viability of different types of germinal differences. Ultimately it might lead to a method of selectively eliminating certain undesirable types of germ cells. The studies of Pearl on the effects of alcohol on pure races of fowls, of Harrison with moths, and other similar results, indicate in such cases there is a selective weeding out of weaker germ cells, leaving the stronger to take part in development.

Gilmore (1927) described a family with a brachydactylous condition very similar to those previously described. There are only two phalanges in each finger, the proximal ones being of normal length, the distal ones abnormally short. The nails are rudimentary, not extending to the ends of the fingers. The thumbs had only one phalanx, with a shortened nail. The feet were normal. A laborer suffered no disability from this condition. The inheritance is a simple dominant with 13 cases (7 ♂ 5 ♀) in four generations.

Chilton (1927) described a pedigree with six cases in four generations, in which the middle and terminal phalanges were shortened, and each finger had *two nails* side by side separated by a strip of ordinary skin. The thumbs show the condition most completely and the little fingers least. The feet were normal, inheritance dominant.

Hereditary *shortness of thumbs* was first described by Breitenbecher (1923) in a family in Oklahoma. The terminal phalanx of the thumbs is very short with a very broad and short nail, and measurements show that the second phalanx of the other digits is also shorter than normal. The metacarpals, however, are longer than in normal hands. Women with such short thumbs found it necessary to use a short needle in sewing. The condition is traced as a simple dominant through five generations. Nine of the children died in infancy. Of the remainder, twelve are seen to be abnormal and fifteen normal, in sufficient agreement with a 1 : 1 ratio.

Hoffman (1924) has described the same hereditary conditions in two women. In each case a sister and the maternal grandmother showed the same condition. Hence it was an irregular dominant. Hoffman (1928) described eight more cases, six of them bilateral. It was also present in relatives and ancestors. Thomsen (1928) described the short thumb in Sweden as due entirely to shortening of the distal phalanx, owing to too early ossification of the epiphysis in this phalanx. The nail again is very broad and short (Fig. 140), and the condition is not associated with long and narrow hands. Thomsen reports it in fifteen "unrelated" families. It is an irregular dominant. The condition is also frequently unilateral.

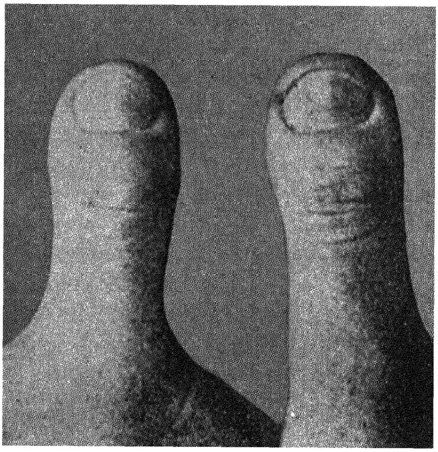


Fig. 140. Short distal phalanx of thumbs, with short, broad nail. (After Thomsen)

Short thumbs similar to those of Breitenbecher's pedigree appear to be of fairly common occurrence. They stand on the border line between an abnormality and the normal condition. Hefner (1924c) finds a short terminal phalanx of the thumb in nine separate lines in Ohio and gives one pedigree of the condition with fifteen cases in five generations (Fig. 141), and two others each with four cases in two generations. The condition sometimes occurs in only one hand. In one individual it was sporadic, his four sibs, parents, grandparents and numerous aunts, uncles and cousins all being supposedly free from it. This is probably a case of mutation.

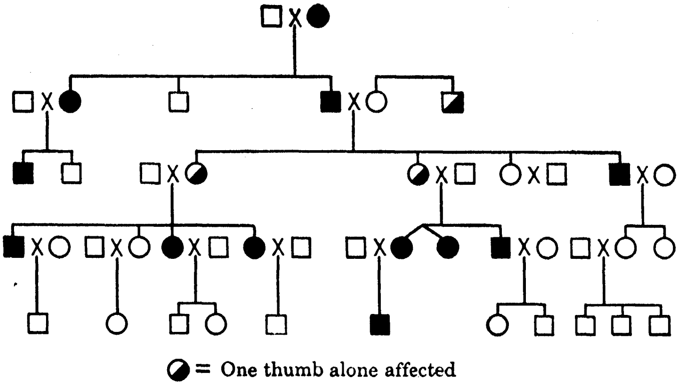


Fig. 141. Inheritance of short thumbs. (After Hefner)

Hefner also refers to a case where father and son have a peculiar condition of the little finger, which cannot be straightened owing to *shortness of the tendon.* The proximal phalanx is also bent at the tip. Neurath (1932) recorded a family with broad thumb and big toe, with a broad nail. There were five cases in three generations (dominant), the thumbs and big toes being affected in all. Sayles and Jailer (1934) described another family with short, broad thumbs and a wide nail.

The condition was strictly dominant, with eight cases in four generations. It appears to be fairly common in the population.

Still another form of digit shortening is that in which the phalanges are of normal length but the metacarpals or metatarsals or certain of them are abnormally short. For this condition the term *brachymetapody* has been suggested. In a family described by Gillette (1931), the third (ring) finger on each hand is affected, the metacarpal for that finger being very short, so the tip of the ring finger is scarcely beyond that of the little finger. It was a somewhat irregular dominant, with 6 cases (1 ♂ 5 ♀) in three generations. The third digit was also short in one individual, the fifth in another and the fourth toe on the left foot in a third. Koenner (1934) shows (Fig. 142) a single case in one hand of a man whose parents and grandparents were normal. Stiles (1939) cites thirteen papers on this condition, the earliest in 1903. They are mostly isolated cases without reference to heredity. How many are real mutations it is impossible to say. Boorstein (1926) found a family in which a short metacarpal, generally fourth, was associated with a short fourth metatarsal. Although no pedigree was given, the condition was evidently dominant, with ten cases in three generations. Miskolczy (1929) recognized it as dominant in a family in Budapest

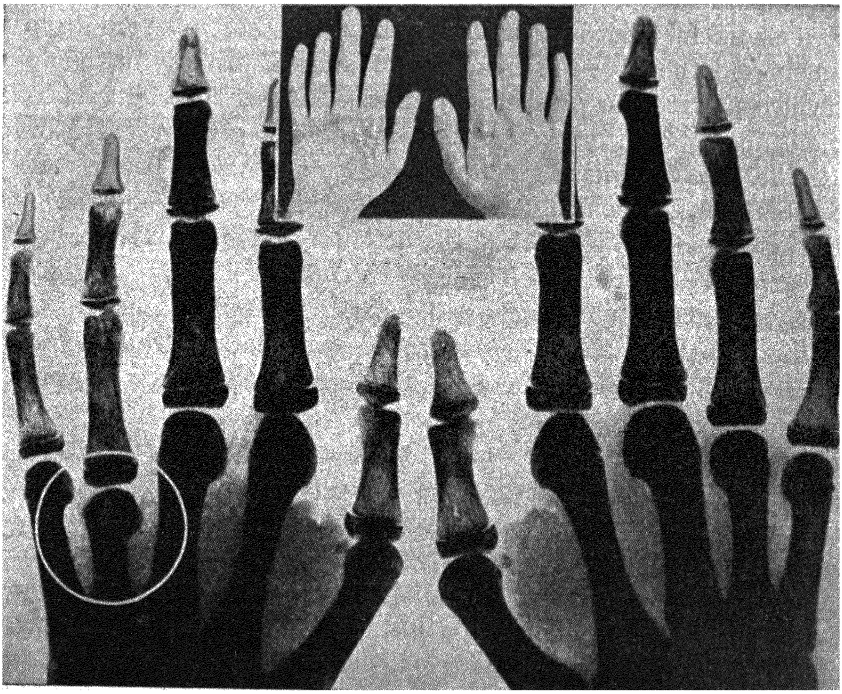


Fig. 142. A short metacarpal. (After Koenner) (From the *J. of Heredity*)

with eight cases in three generations. He calls it *brachymetacarpy* and finds it linked or associated with schizophrenia in the same family. Metacarpals III and V were short. Stiles' family had 5 cases (1 ♂ 4 ♀) in two generations, the dominance irregular. Brailsford (1945) gives skiagraphs of a family with 18 cases in four generations. Metatarsals or metacarpals III, IV and/or V were short, and some had associated defects of the bones.

Davenport (1933) cited a family in which it was at first alleged that a short metacarpal (depressed knuckle) had resulted from an accident and then been transmitted to a child. It was finally found that the condition was present in mother, daughter and a second cousin (female), being most marked in digit IV but also present in III and V. Steggerda (1942) describes a family in Yucatan, with three cases in two generations, in which the fourth metatarsal only is short, making the fourth toe no "longer" than the little toe. It is probably dominant with very low penetrance. Fischer and Vandemark (1945) cite a soldier with both fourth metacarpals and fourth metatarsals short, causing pain in marching. This was associated with dark brown pigmented areas on trunk and legs. There is no basis for their suggestion that the condition is recessive.

This and much other evidence shows that single bones of the skeleton can be controlled by a single gene, either as regards their length or their complete absence. Particular muscles are also frequently present or absent. The variability in the expression of the above gene is shown by its unilateral occurrence, irregular dominance and the occasional affection of adjacent metacarpals and of metatarsals. It also appears to find expression more frequently in the female sex.

Many military cases of painful feet owing to a *short first metatarsal* (Morton's syndrome) are described by Bingham (1944), but no evidence of its manner of inheritance is offered. In recording 259 cases of fractured metatarsals from marching, Leveton (1945) finds that the condition occurs mostly in soldiers of 18 to 19 years with normal feet. He finds it more frequent when the metatarsal is rather thick, and attributes it to fatigue of the peroneus longus and the tibialis posticus muscles, which help to maintain the arch of the foot.

It is generally recognized that the more marked forms of brachydactyly are accompanied by shorter stature, the long bones of the skeleton being affected. Shafar (1941) summarizes the various forms of finger-shortening and adds another in which the *shafts of the metacarpals and metatarsals as well as the phalanges are shortened and broadened.* Although the fingers and toes are short, there is no lack of manual dexterity, but the head of the femur is flattened and irregular, causing difficulty in walking. Radiography showed that the epiphyseal ossification was irregularly multinucleate, leaving small unfused ossicles. This is really chondro-osteo-dystrophy in hands, feet and hips. Five cases, all female, were found in three generations, the condition dominant.

Short fingers and wide hands are inherited in a family with eighteen cases in four generations and one skip (Pendergast, 1936), but the anatomical conditions were not determined.

In Swedish cattle a condition is described (Johansson, 1942) in which the metacarpal and metatarsal bones are shorter than normal, phalanges I and II are missing, but phalanx III and the hoofs are normal. These animals cannot stand, but crawl, and the condition is probably a monogenic recessive.

Crooked Little Fingers

Lucas (1880) says, "I have more than once traced a crooked little finger through three generations." Pol (1921) made an extensive anatomical investigation of brachydactyly and related digital abnormalities, such as *clinodactyly.* He regards the latter as an intermediate step between biphalangy and triphalangy. These anomalies are classified into two types, differently inherited. In brachyphalangy and hypophalangy only the malformed transmit the deformity, i.e., it is dominant, while in brachyhyperphalangy the transmission is also from normals (hence recessive or showing variable dominance). It appears best to use the term *clinodactyly* for fingers bent in the radial direction, and confine the term *camptodactyly* to fingers permanently bent in the direction of flexure. These conditions may be due to the shape of the bones or their joints or may be caused by short tendons. Now that there are so many different forms of inherited short or crooked fingers, the whole subject of their nomenclature requires the careful attention of the anatomists. Vidal (1910) had a pedigree in five generations of abnormal segmentation of fingers. It showed ten cases of brachydactyly in digits II and III with hyperphalangy of II and twenty cases of a bent little finger (seventeen bilateral) as well as other malformations. The condition was dominant with certain skips. Nowak (1934) described a family with clinodactyly, the terminal phalanx of the little finger being bent against the ring finger. It is dominant, with 13 cases (9 ♂ 4 ♀) in four generations. Two smaller families were also recorded. In another case (Cohn and Ravin, 1941) a child of apparently normal parents had clinodactyly of the index fingers and the big toes. This is probably a mutation, but might be recessively inherited. Zurukzoglu (1929) described a family in Bern with 30 cases (16♂ 14♀) in three generations, strictly dominant.

An extreme form of *camptodactyly*, in which the little finger is so strongly flexed that the first and third phalanges are parallel and practically touching, was described in a family (Fig. 143) from the Transvaal (Fantham, 1924). The abnormality is apparently confined to the left hand; it occurs only in males and is transmitted from father to son, like the Y-chromosome. All the sons of an affected father should show the condition unless there is crossing-over between X and Y. In that case, some normal daughters might transmit, but there is no statement regarding this point. The five normal sons might be due to failure of penetrance.

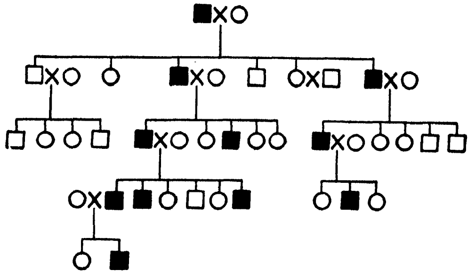


Fig. 143. Pedigree of camptodactyly confined to males. (After Fantham)

A slight degree of camptodactyly was found by Moore and Messina (1936), the little finger only involved and seven of eight cases in three generations unilateral. The condition is dominant, with one skip. The joint is normal, the little finger being permanently extended in some and permanently flexed in others. It is supposed that the extensor expansion, which trifurcates, has longer and weaker lateral parts, causing permanent flexure in some and extension in others. Thomas (1936) described three unrelated cases of girls in which the little finger of both hands had the terminal phalanx elongated and curved inward toward the palm.

Manson (1928) described a man with the fingers of both hands deviated toward the ulnar side (clinodactyly), hollowing of the palms, and a very prominent first carpo-metacarpal joint. His feet were similar. He inherited the condition from his mother, who showed the condition in her feet but had normal hands. His sister was like the mother, while two brothers were normal. He had a son who was normal, a daughter with high plantar arches but normal hands, and a younger son with plantar arches in both feet.

Hefner (1929) recorded the occurrence of crooked little fingers due to congenital shortness of the branch of the flexor digitorum ligament leading to the middle phalanx of the little finger, and suggested for it the name *streblomicrodactyly* (Fig. 144). This is then a form of camptodactyly, and 14 cases (5♂ 9♀) in four generations of a family were recorded, the condition being strictly dominant and confined to the little fingers, occasionally unilateral. Allan (1939) found the same condition in a family with four cases (all males) in three generations. The dominance is very irregular and there may be a predilection for the male sex. Allan has three other pedigrees of ***short finger tendons.*** In family B the condition is the same, the inheritance dominant with four females affected in three generations. This confirms the excess of females affected in Hefner's family. In family A, that part of the extensor digitorum communis tendon inserted into the dorsal surface of the last phalanx of the *ring finger* is so shortened in both hands that the last joint can be only slightly flexed. That the joints are otherwise normal was shown by X-ray examination. The family had 7 cases (3♂ 4♀) in three generations, inheritance dominant with no skip. In family C a boy could not extend his *middle fingers* beyond a right angle at the middle joint owing to shortening of the tendon of the flexor digitorum sublimis which is inserted into the sides of the second phalanx. His brother had the same anomaly in the ring fingers, and their mother in the little fingers. Inherited tendon defects thus show the same specificity and limited variation in the fingers affected, as is found with abnormalities of the phalanges and their joints.

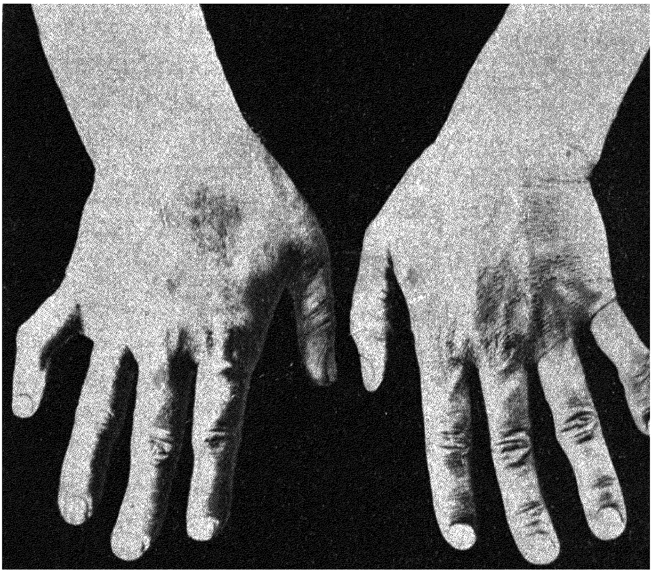


Fig. 144. Camptodactyly due to a short ligament. (After Hefner) (From the *J. of Heredity*)

Ritterskamp (1936) described a family with six cases of camptodactyly in three generations. Contracture of the little finger of one or both hands occurred at the basal joint (cf. Dupuytren's contracture). The inheritance is dominant, with one skip. Frequently the third finger was involved and *hammertoe* was an associated condition. The many theories of the origin of this condition include a dermatogenous theory (primary lack of skin differentiation), desmogen theory (contraction of connective tissue and tendons), myogenic theory (origin in the muscle) and an arthrogenic theory (changes in the joint), but all agree that it is inherited. Another family was described by Hefner (1941) with slightly crooked little fingers (minor streblomicrodactyly), 12 cases (4♂ 8♀) in four generations, strictly dominant. Dolichodactyly (long fingers) is noticeable in the hands and the slight crook of the little fingers appears to result from a short tendon of the flexor digitorum muscle. Some of these conditions may be allelic, but there is no evidence on the point.

Goldflam (1906) reported a family in which the little finger and in some cases also the ring finger was flexed, with ankylosis, so that objects could not be grasped. Hefner (1924b) recorded a case in which the little finger in each hand was crooked owing to short tendons and also to a bent tip of the first phalanx. The same condition was present in one hand of the father. Stoddard (1939) records a family with 11 cases (4♂ 7♀) in four generations (unilateral in three) of a crooked little finger due to a short tendon. In one case the defect was corrected by massaging and so stretching the tendon.

A well-known Roumanian pedigree (Fig. 145) of Tomesku (1928) is believed to show genetic linkage between a crooked little finger (clinodactyly) and brunet coloring. The terminal phalanx was bent to the radial side and digits II and IV were similarly affected to a less extent. The sixteen cases in four generations were all said to have black hair, while those with blond or brown hair did not have clinodactyly. This would indicate close linkage. Tomesku cites Weber (without giving the reference) as observing a family in which the members with red hair had exostoses while the brunets did not. Glass and Magee (1935) cite a family with four cases of bent little fingers in four generations, the second phalanx of this finger being short and the joints all flexible. Three of them had dark brown and the fourth red hair. In another family the grandfather had crooked little fingers, which reappeared in different sibships of the third generation. A blond member of this family had the clinodactyly. This evidence is not sufficient to prove an absence of linkage.

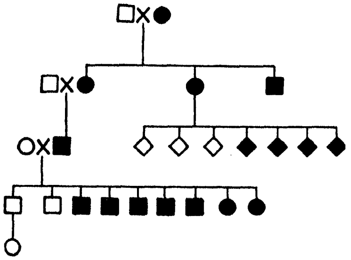


Fig. 145. Linkage of clinodactyly and brunet complexion. (After Tomesku)

A combination of *biphalangy* (two phalanges) with lack of nails (*anonychia*) on certain fingers, and *ankylosis* of the distal interphalangeal joint of digit II, was described by Drey (1912). The pedigree shows dominance, with 10 cases (4♂ 6♀) in five generations. Probably two independent or partially linked genes are involved. There were four cases of biphalangy, three of a stiff joint and four of both together.

Several cases of hyperphalangy combined with other digital defects have already been mentioned. A special form of hyperphalangy is a *three-jointed thumb*. Stieve (1916) described a case in which the thumbs of both hands had an extra joint. This is one of the rarest malformations of the hand, due to failure of the two terminal phalanges to fuse.

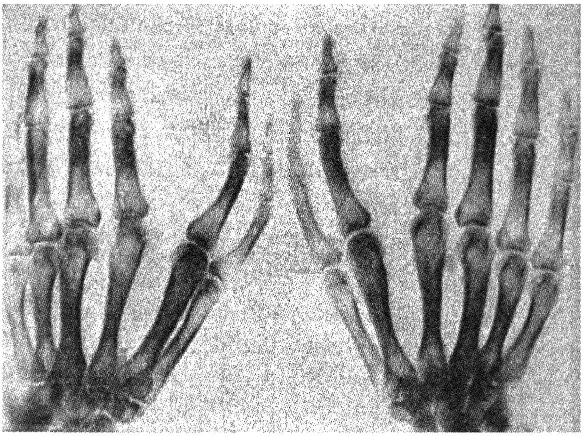


Fig. 146. Skiagraph of hands showing the thumb replaced by two fingers, each having three phalanges. (After Penhallow)

He cites thirty-nine cases from the literature, in which there is a supernumerary phalanx on both thumbs, and sixteen in which it is on only one hand. In thirty-three cases of its bilateral occurrence, in ten different families, it was known to be inherited, while there was said to be no evidence of its inheritance when it occurred on only one hand. Rieder (1900) described a family in Munich in which an affected father had an affected daughter by his first marriage and three of five affected children by his second wife. The condition was evidently dominant. The middle phalanx of the thumb varies greatly in length in these cases. Roberts (1943) describes another family with three-jointed thumbs on both hands, strictly dominant, 14 cases (6♂ 8♀) in four generations. He cites several other families from the literature.

Frere (1930) described a Negro family with this condition in three generations, each hand having two thumbs, each with three phalanges. Penhallow (1928) described a single case in a colored man (Fig. 146). The thumb of each hand was replaced by two functioning fingers, each having three phalanges and resembling the third and fourth fingers.

The nails were perfect and there were six metacarpals. These two fingers were perfectly formed and functioned independently. The left foot also had a double great toe, only the two terminal phalanges being duplicated. Polonskaja (1936) described two unrelated cases of double thumb on one hand, one of them in a Bashkir. They were combined with various defects of heart, arteries and intestines. Smith and Norwell (1894) described an early family with three-jointed thumbs and polydactyly, eight cases in three generations (dominant).

From the cases cited by Stieve it is evident that a three-jointed thumb, when present bilaterally, is inherited as an irregular dominant. In several cases hyperphalangy of the thumb was combined with radial polydactyly, i.e., doubling of the thumb. In one family, father and daughter both had two three-jointed thumbs on each hand. Probably when these conditions are unilateral they are still inherited but show much lower penetrance.

Schroeder (1918) described a condition of *hypodactyly* appearing in the hands and feet of a family for five generations and accompanied by other deformities. The strain originated with a woman, who is said to have had normal parents. She produced three affected and two normal children, the latter having only normal descendants, while the former had 28 normals : 16 affected offspring. The condition is transmitted by both sexes, and shows a tendency to become less marked in later generations.

A valuable study of *brachydactyly* and related conditions was recently made by Schinz (1943), who brings together the pedigrees and sketches the anatomy of hands and feet. He recognizes four main types:

1. Farabee (brachyhypophalangy of hands and feet, with little variation).
2. Drinkwater I (brachymesophalangy and brachyhypophalangy, with much variation).
3. Drinkwater II (brachymesophalangy with little variability).
4. Vidal (1910) (brachyhyperphalangy with inherited variations).

These are all simple dominants with variation in expressivity and Schinz makes the probable suggestion that they are polyallelic. He also classifies as follows the forms of brachydactyly occurring in *one* finger only:

1. Brachydactyly V, short little finger, due to brachymesodactyly (short middle phalanx). In some families the finger also shows clinodactyly.
2. Brachydactyly II (short index finger, brachymesophalangy of the Mohr and Wriedt type). In some families brachyhypophalangy of the index fingers is also present, with much variability, and the homozygote is a severe malformation.
3. Brachydactyly II and V (no pedigrees).
4. Brachydactyly I (short thumb). Very frequent and very variable.

5. Brachymetapody (one or more short metacarpals or metatarsals). Stiles' (1939) pedigree shows five cases of short metacarpal IV in two generations. This condition is sporadic, variable and often combined with brachyphalangy.

Polydactyly

Polydactyly is a part of the general phenomenon of reduplication of parts. Examples range from complete reduplication of a limb or part of a limb to doubling of a single phalanx of the little toe. The significance and relationships of the various forms and degrees of polydactyly are, however, not yet clear. Polydactylism is found not only in man and monkeys but in horses (a reversion), cattle, dogs, cats, guinea pigs, fowls and other animals.

In hexadactyly, which is the usual form, the extra finger may be on the ulnar or postaxial side of the hand, i.e., an extra little finger. Praeaxial or radial hexadactyly, duplication of the thumb, is, according to Müller, more frequent and cases have already been mentioned of its combination with triphalangy of the thumb. Radial and ulnar polydactyly may occur together in the same family. They are probably controlled by separate genes, which are perhaps allelic. Both pre- and post-axial polydactyly appear in several main types: (1) Most common; the extra digit is a small attachment not adherent to the skeleton and often without bones or cartilage, muscles or tendons. (2) The extra digit is often more or less like an ordinary finger or toe, containing bones and connected with the skeleton of the finger. (3) Very seldom the extra digit is complete and may even have its own metacarpal or metatarsal bone. All possible intergrades occur between these forms.

Polydactyly was known in classical times. Pliny refers to a Roman poet named Volcatius with six fingers on each hand, who received the surname Sedigitus. He also states that two daughters of a Roman noble had each six fingers and they took the name Sedigitae. Similarly Flaccus referred to pendulous ears, and there are numerous other descriptive nicknames in the classical writers. Still earlier, the giant of Gath (II Samuel XXI: 20) had six fingers and toes, at a time attributed to 1019 B.C. Bell (1930) cites other early references. Morand (1773) gives practically all the information available on the subject up to his time. Gruber (1870) found in the literature 127 cases of hexadactyly in 13 or 14 families. In 52 of these the thumb or big toe was doubled, in 75 the little finger or toe, and in no case were other fingers duplicated. In a pair of female twins (apparently identical), one had 6 fingers, the other 6 fingers and 6 toes. In modern times the family of the Sultan of Pontianak (Borneo) was hexadactylous and regarded the condition as a mark of royal distinction! According to Daisy Bates (1939), in the 1860's a group of Australian aborigines existed with six fingers and six toes in the region between Eucla and Lake Eyre. They had come from the Petermann Ranges, were seen by Helms and have since intermarried with pentadactyls and become extinct. She also "often encountered" left-handed groups and believed the condition inherited.

An early hexadactylous family is described by Carlisle (1814). Zerah Colburn, the son of Abiah Colburn, born in Vermont, was brought to London on account of his "extraordinary powers in arithmetical computation from memory." He had a supernumerary little finger on each hand, and an extra little toe on each foot. The extra digits were all perfectly formed, with nails and three phalanges. The father also was hexadactylous, having five metacarpal bones, but six metatarsals. The pedigree of this family through four generations is given in Fig. 147. Beside each is given (above) the number of fingers and (below) the number of toes. The inheritance is strictly dominant, with occasional failure of one hand or foot to exhibit the abnormality. If the original family of eleven children were all hexadactylous the mother must have been homozygous. This seems improbable.

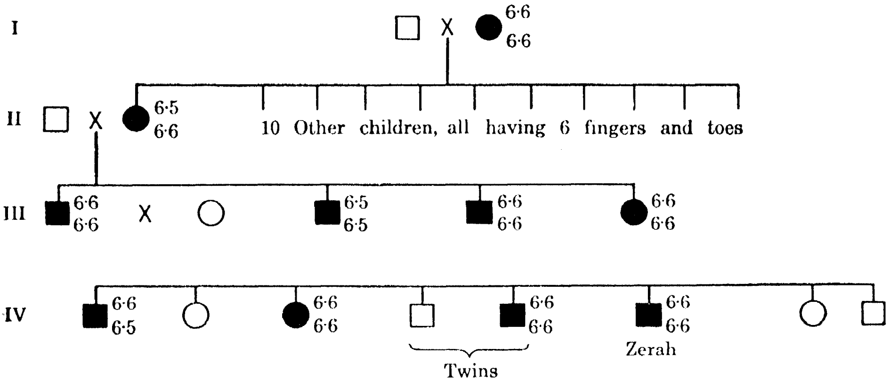


Fig. 147. Pedigree of dominant hexadactyly. (After Carlisle)

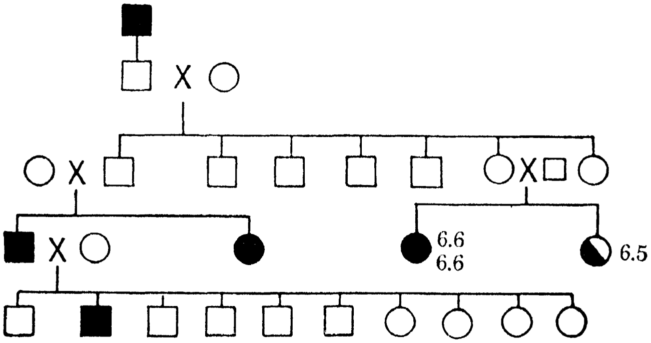


Fig. 148. Irregular dominant pedigree of hexadactyly. (After Sedgwick)

In another hexadactylous family (Sedgwick, 1863, p. 188) an extra finger with two phalanges and a nail was attached to the base of the first phalanx of each little finger. The condition was followed through four generations. There was some variation in its expression, and it skipped two generations both in the male and the female line (see Fig. 148).

Clement Lucas (1880) compiled from Suffolk a family of polydactyly (Fig. 149), here thrown into modern pedigree form, with some remarkable features. Extra little toes occurred more frequently than extra little fingers, and two brothers had seven toes. There were 26 cases (12 ♂ 8 ♀ 6 sex unknown) in six generations, inheritance strictly dominant, sibships 23 affected : 33 normal. Syndactyly was also frequent, in some cases between all the toes; there were also two cases of harelip, one of them having also cleft palate. It would be a boon if all modern pedigrees were collected with equal care.

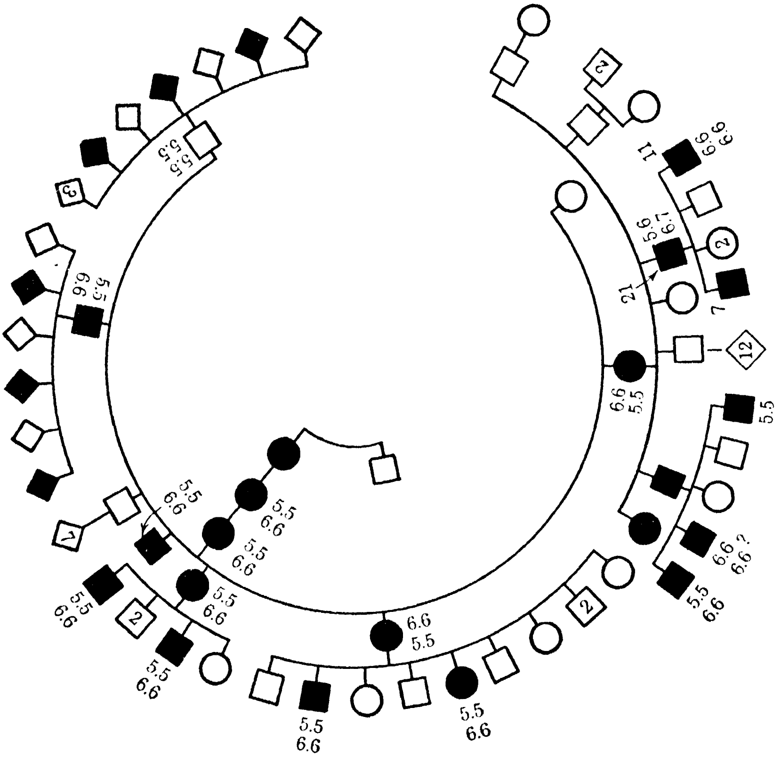


Fig. 149. The Clement Lucas pedigree of dominant ulnar hexadactyly.

Polydactyly in the feet is apparently due in some cases to an extra digit interpolated between digits IV and V. The more complete the polydactyly, the greater is the tendency to syndactyly. Hence they are frequently regarded not as separate characters but as expressions of one factor. The presence of sesamoid bones in these hands (as is frequent in embryo hands) indicates that the processes of absorption are below normal. Since the webbing also indicates a failure of absorption, syndactyly may be regarded as a failure to complete development. In the human foetus the toes are webbed at forty to fifty days and this is more extended between digits II and III than elsewhere. At sixty days only a slight webbing remains at the base of the toes.

Ballowitz (1904) collected many data concerning hyperdactyly, with several pedigrees of dominant polydactyly, but without recognizing the Mendelian explanation. Records of extra fingers and toes are known in many races and no doubt they occur in all, perhaps with varying frequency. The slightest degree, doubling of a terminal phalanx, is most frequent. The outside digits, little finger and thumb, most commonly show duplication. Doubling of other digits is much more rare, becoming still more so as the number of digits increases. Thus the presence of ten digits on one hand or foot is extremely rare in museums, while cases of seven are relatively often described. Polydactyly is often combined with other abnormalities, but hexadactyly and heptadactyly frequently occur in otherwise normal individuals.

Polydactyly is still endemic in certain localities. De Linares (1930) visited a village near Madrid with a population of 150 in which every person was said to be polydactylous. The mayor had hands "like a crab's pinchers." Some had seven perfect fingers. Generally the thumb was duplicated. One person had twenty-two, another twenty-six digits. The visitor saw over a hundred persons, all having six fingers on each hand, but there was an occasional hand with only five fingers. Boinet (1898) says it is reported that in the Foldi family of the Arab tribe of Hyabites hexadactyly is so general that any child born with five fingers is regarded as "adulterin" and immediately sacrificed. Lücker (1924) recorded a secluded German village with frequent consanguinity and endemic polydactylism and harelip. Ballowitz (1904) quoted from the French literature (1863) the case of an isolated village in the Département d'Isère in which, through inbreeding, nearly all the inhabitants were said to have six fingers and toes. Later, owing to increased communications, marriages with normals took place and the polydactyly is said to have disappeared. This would not happen in the case of a dominant character, and Odiorne (1943) has pointed out that the story of this village is false. In brachydactyly, on the contrary, exogamy always takes place, yet there is no weakening in the expression of the character. The disappearance of such endemic characters requires much fuller analysis.

Atwood and Pond (1917) described a family with dominant inheritance of radial hexadactyly, nine cases in three generations. The thumbs and great toes were generally doubled. This condition was unilateral or incomplete in some individuals and in two cases there were no extra digits but the thumbs had three phalanges. Brandeis (1915) described a family (Fig. 150) with 12 cases (5♂ 7♀) of ulnar polydactyly in four generations. There are several cases of failure of penetrance. Cases III. 4, 5 were both normal, but cousins. Their two children were both polydactylous, so the gene behaved here essentially as a recessive. These two children both had six fingers and toes bilaterally, but were perhaps heterozygous. The extra toe was attached to the fifth metatarsal. Brandeis quotes the family of Struthers (1863) with nine cases in five generations, and Fackenheim (1888) with twenty-three cases in four generations. Sinha (1918) recorded a Bengal family with double thumb. There were only three cases in three generations, the sibships numbering 2 affected : 21 normal. This probably means extremely low penetrance of the dominant gene. Milles (1928) published a number of pedigrees of polydactyly and other abnormalities In one family with 13 cases (9♂ 4♀) in three generations, a small fleshy mass with remnant of a nail is attached at the base of the little finger or toe, and the end of the metacarpal or metatarsal bone was enlarged to receive it. The inheritance was strictly dominant. Another pedigree showed twelve cases in three generations. Orel (1928) has a pedigree of doubled thumb, strictly dominant, with 18 cases (11♂ 7♀) in five generations. In another family in Austria, with ninety-three members descended from a pair through five generations, only two polydactyls appeared (extra little finger and toe), one in the second and one in the fourth generation, so it must be recessive or at least of extremely low penetrance.

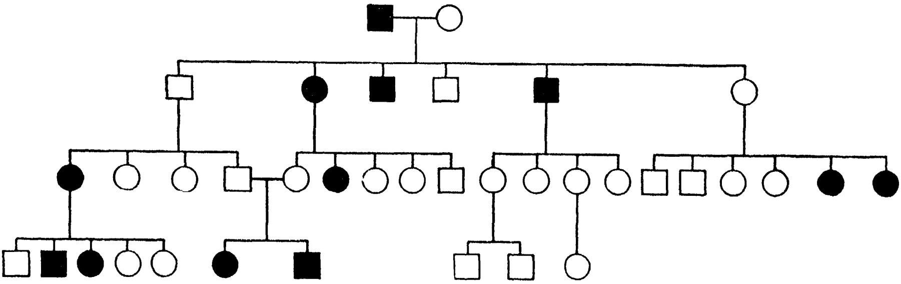


Fig. 150. Irregular dominant pedigree of ulnar hexadactyly. (After Brandeis)

Sysak (1928) investigated polydactyly in a group of villages in the Ukraine where many families are affected. They show irregular dominance, both double thumbs and double little fingers sometimes in the same person, producing as many as seven or eight fingers. In 12 small pedigrees there were 34 affected males to 31 affected females, the sibships numbering 44 affected to 19 normals. The large excess of abnormals is probably not all explainable by a difference in ascertainment, and there is some indication that the germ cell carrying the gene for polydactyly may be stronger than the normal.

Bell (1930), besides citing the early literature, has a dominant pedigree showing 16 cases (6♂ 10♀) in five generations (7 having also syndactyly) of doubling chiefly of the thumb and big toe. In certain cases the little finger was also doubled, so both prae- and post-axial duplication were present. The sibships number 15 affected : 7 normal, again a large excess of affected. In another pedigree (2) the hands have generally an extra little finger, the feet generally an additional little toe, and there is no syndactyly. The inheritance is clearly recessive. There are only six cases in three generations, the two sets of parents were normal, and the sibships 6 affected : 16 normal. In Cockayne's case (4) the polydactyly was associated with retinitis pigmentosa and hypopituitarism. There were only three affected sibs from normal parents, so the genetic relations remain unknown. Aschner (1929) made an extensive study of skeletal defects from the literature. A pedigree (after R. Pott) of radial deviation and *doubling of the end phalanx of the thumb* with, in some cases, a doubled thumb nail, shows dominant inheritance with 11 cases (4♂ 7♀) in three generations. A family with polydactyly and syndactyly shows 21 cases (11♂ 10♀) in four generations, with one skip.

Bonnevie (1919) described a type of postaxial polydactyly in man, which is usually stronger on the right side of the body. The extra finger arises from the base of the little finger, the metacarpal bones being normal. There is much variation in this abnormality, and families showing it are now distributed all over Norway, but they are all probably descended from the same ancestor about three hundred years ago.

Sverdrup (1922) carefully analyzed a Norwegian family with dominant postaxial polydactylism in six generations, beginning with a woman living about 1800. An extra little finger or a portion of one is present. This is associated with brachydactylism, apparently due to shortening of the metacarpals and metatarsals. Sometimes it occurs in one hand and both feet, or it may be in one hand and one foot, or only in the hands. The extra digit varies from a wart-like appendage to a complete finger or toe with metacarpal, phalanges and nail. Two types of the condition are recognized, with intergradations. A consists in the duplication of a digit, usually V. In the B type a small appendage is loosely attached to the ulnar border of the hand, and there is no shortening of the metacarpals, but people with B type hands have A type feet. A type parents can have B type children, but B type parents cannot have A type children. All the polydactyls are heterozygous, and 12 families from DR × RR matings produced 34 polydactyl : 23 normal siblings. One line of descent belongs mostly to the A type, another entirely to the B. The B type is produced by a single factor, and the A type is probably due to an additional modifying factor.

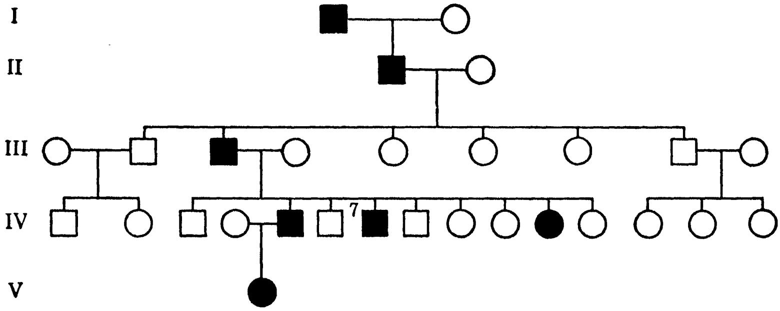


Fig. 151. Inheritance of double thumbs with three joints in the Scipion family. (After Manoiloff)

Probably the most remarkable "pedigree" on record for its length is that of hexadactyly in the Scipion family (Manoiloff, 1931). The last five generations are represented in Fig. 151 and the hands of IV. 7 are shown in Fig. 152. It will be seen that the thumbs are duplicated and the radiogram shows that they all contain three phalanges. The feet were similar, one of them having digit II very broad, with two nails (Fig. 153), so this foot had essentially seven toes. Case IV. 7 was an engineer at Batoum and according to the pedigree in the possession of the family, this peculiarity had been transmitted in his family for about seven hundred years. An ancestor emigrated from Italy to Poland with the retinue of the Italian princess who married the king of Poland. His descendants continued to live there. Adam Josifovič (II. 1), born in 1813, was banished to Siberia, where he married a

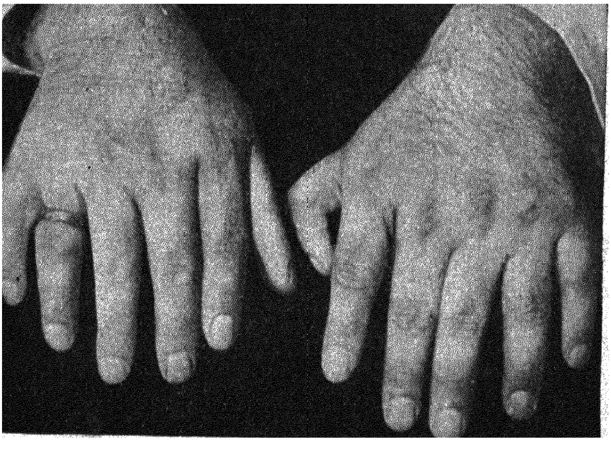


Fig. 152. Hands of IV. 7 in Fig. 151. (After Manoiloff)

Russian woman. It is stated that until generation IV the hexadactyly had been transmitted only in the male line. This would mean inheritance in the Y-chromosome, but it is unlikely that crossing-over would only begin after many generations without it. More likely the condition is, as usual, a simple dominant; but on the other hand, the transmission of the defect with the surname Scipion for some seven hundred years would be more likely if it were only in the male-to-male line of descent.

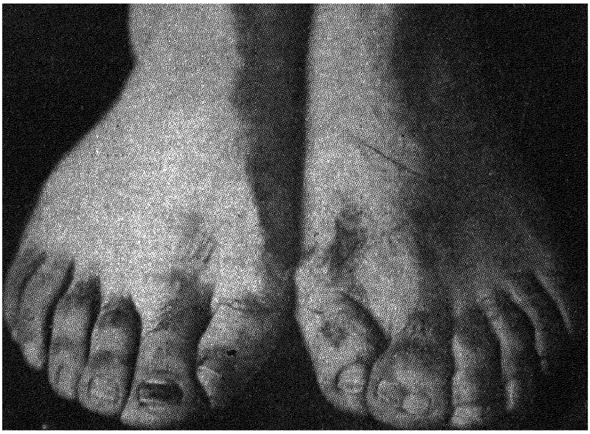


Fig. 153. Feet of IV. 7 in Fig. 151. (After Manoiloff)

The origin of the family is said to have been traced to Scipio Africanus (237–183 B.C.) who, "according to historical data" had likewise six fingers and six toes. If these statements can be verified, it would follow that hexadactyly had been transmitted in this line for over two thousand years and that the name of Scipio had survived through some eighty generations.

Zirkle (1936) cites an observation of Sir Kenelm Digby in 1645. A woman in Algiers had two thumbs on her left hand. Her four daughters and the eldest daughter's daughter were seen to be in the same condition although the sons were normal. The mother's mother and grandmother were stated to have the same feature. The condition thus appeared in the females (at least eight) of five generations and therefore the family might possibly have linked XX chromosomes. But considering the state of observation at that time it was probably a case of simple dominance.

Just as families can differ greatly in the degree of expression of polydactyly, so they can differ in the degree of dominance of the character. Kemp and Ravn (1932) describe two pedigrees: one fully dominant with forty-one cases in six generations, the other showing variable dominance. Nylander (1931) has a pedigree with forty-one cases of prae-axial polydactyly in five generations, two to five thumbs on each hand. Ménaché (1931) has one of three generations in which the six affected members all have six fingers on each hand and six toes on each foot. Some had two thumbs, some two little fingers, and some were also syndactylous. Brody's (1934) pedigree had in one family only a doubled little toe, in another an extra little finger as well. The two families were united by marriage. The fifth metatarsal bone took the not uncommon form of a Y with a toe on each branch. This condition is illustrated from skiagraphs in *J. Hered.* 7 : 322–332. The pedigree is very incompletely recorded, but it shows direct descent in five generations. Jackson's (1937) pedigree, with fourteen cases in four generations, shows one skip. Either hands or feet or both could have six digits. As one child had a vestigial sixth finger removed, the hexadactyly was evidently of the post-axial type. Family tradition traces the condition back four generations further to a very strong woman with six fingers and toes.

Rudert (1938) records a case of doubling of the terminal phalanx only of the thumb in two brothers and a sister and its bending toward the ulnar side. The bending alone is found in ten other members of the family, tracing back to a common ancestry in the fifth generation. This doubling is probably a dominant of very low penetrance, while the bending has a higher penetrance.

In the Thüringian forest a boy of twelve and his sister had the same malformations: very broad, short hands with syndactyly of digits II–V, the end phalanx of IV bent radialwards and of II and III ulnarwards. Both hands were alike, the thumbs abnormally broad in the terminal phalanx and nail. Toes II–V were also syndactylous, the big toes fully doubled. The boy also had tower skull and adiposo-genital dystrophy. All the ancestors and collaterals were normal for four generations back. The condition could be described as acrocephalopolysyndactyly and was evidently recessive.

Odiorne (1943) gives a striking pedigree of polydactyly in six families all descended through ten generations from a single man born about 1620 who emigrated to New England. His descendants include ninety polydactyls, the present families living in various parts of North America. The condition varies in different families or lines of descent within this complex. In family 3 it is strictly dominant and fully expressed, all affected individuals having six digits on each extremity, and the affected to unaffected number 2 : 1, though this may be partly due to incomplete ascertainment of the normal individuals. Families 1 and 5 also show complete penetrance, but the ratios are near the expected 1 : 1 and there is considerable variation in expressivity. In families 2 and 4 there are skips (failures of penetrance), the ratio of affected to normal is low and there is variable expression. In family 6, some information is lacking and the ratio of affected is low, but the expression appears to be uniform although there are certain skips. Variation in penetrance and expressivity is generally attributed to the presence of inhibiting or modifying genes, but as penetrance is an all-or-none reaction it may be environmentally controlled in some cases, and so may the expressivity.

A condition which is closely related to ulnar hexadactyly is the formation of small finger-like excrescences in the ulnar part of the hand. These are known as *pedunculated postminimi* (Fig. 154). Streeter (1930) has shown that there are many cases of intra-uterine amputation. "Sharply circumscribed areas of limb-bud tissue are of such inferior quality that only imperfect histogenesis occurs." They finally are sloughed off in development and are said to be amputated. They are not due to amniotic bands or other agencies external to the embryo, as formerly supposed, but are genetically determined. He described sixteen cases in digits and even larger portions of the extremities, and concluded that they are generally of germinal origin. Circumscribed areas of a limb-bud may develop to twice the normal size owing to growth vigor. At the other extreme a part may be entirely absent. Between these extremes are the cases where a part is of normal size but abnormal formation. By the fourteenth week the areas of imperfect histogenesis are moribund and sloughing away from the normal tissues. At birth, only depressions, grooves or healed stumps with residual strands may remain visible. These defects occur mainly in the mesenchyme and especially the subcutaneous connective tissue. Günther (1939) gives short pedigrees of "amputation," showing other abnormalities among the ancestors. He points out that finger rudiments present on the stump of a limb show that it has not been amputated. True amniotic malformations do occur, but they are extraordinarily rare and whether this tendency is inherited is unknown.

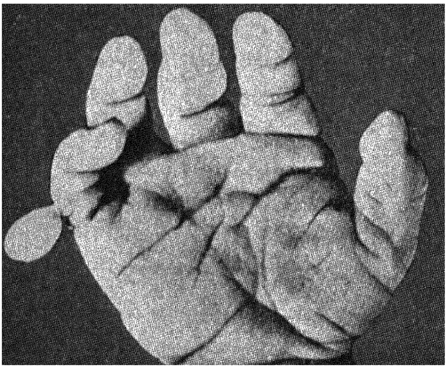


Fig. 154. Pedunculated postminimus with thin pedicle, from female foetus. (After Cummins)

Cummins (1932) has studied fifty-six cases of postminimi, showing their close relation to a polydactylous condition. In twenty-one families some family history could be obtained and fifteen of them showed a positive family history. One Negro family had eight cases of pedunculated postminimi in three generations. The grandfather, I. 2, had a cousin with six fingers and had postminimi on both hands and feet. His daughter had them on both feet and scars of amputation from both hands, and six of her nine children had them. A second Negro family had perhaps eleven cases in three generations, a third family had postminimi, polydactyly and syndactyly. Evidently these are polydactylous families in which the development of the extra finger is arrested when the gene has not sufficient strength to carry it through. Such a gene is possibly distinct and allelic to the one for ulnar hexadactyly.

There can now be little doubt of the existence of recessive polydactyly, although it is very rare in comparison with the dominant form. It is necessary, however, to recognize in polydactyly and some other conditions a *sliding scale of values, from absolute to variable dominance with such a low penetrance that it cannot be distinguished from recessivity.* The distinction is simply that a single dominant gene of low penetrance will sometimes produce a phenotypic effect, while a single recessive gene never will. The most convincing case of recessive polydactyly is that of Shevkenek and Thompson (1933). Figure 155 shows the pedigree of a family of immigrants from Bukovina to Saskatchewan, in which the *little finger is partially duplicated.* This is only a minor expression of the gene for polydactyly, which may have something to do with its recessive behavior. In polydactyly the recessive is the mild form of the gene, whereas in most other abnormalities the recessive is the most severe form. Usually in this family only the terminal segment of the little finger is duplicated, on one or both hands. There is never a complete extra finger, but the condition varies from two joints to a mere "wart" on the ulnar aspect of the hand. It appears that III. 6 and III. 7 were both heterozygous for the gene, and four of their nine children showed the condition. These have married persons from widely scattered regions, with the result that all their eighteen children have normal fingers. If this were a dominant of low penetrance it would not be expected to appear in four cases out of nine. On the other hand, the expectation for a recessive is only four in sixteen.

An instructive pedigree from this point of view is that of Snyder (1929). A Negro family in North Carolina (Fig. 156) shows 44 cases (18 ♂ 26 ♀) in six generations. They are all more or less related and living in one locality. The extra little finger is small (Fig. 157) and is occasionally reduced to a postminimus hanging by a piece of skin. In the pedigree, III. 9–16 with 5 out of 8 affected, is in harmony with a simple dominant through three generations. But III. 16 and III. 17,

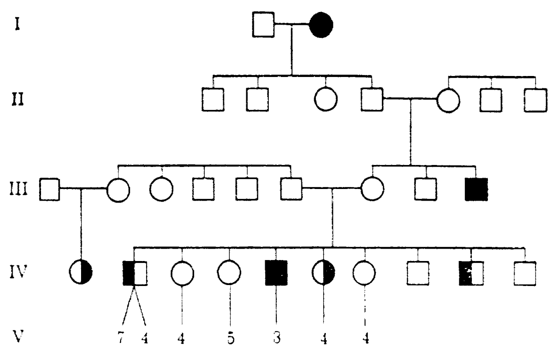


Fig. 155. Recessive pedigree of partially duplicated little finger, on one or both hands. (After Shevkenek and Thompson)

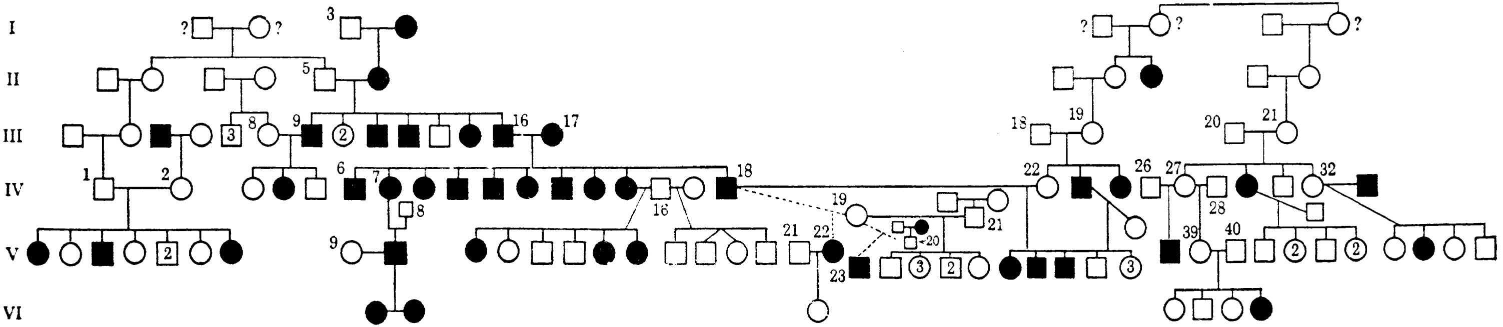


Fig. 156. Pedigree showing a duplicated little finger in a Negro family in North Carolina. The condition is either recessive or more probably dominant with low penetrance. IV. 18 may be homozygous for polydactyly or IV. 19 might be heterozygous, to account for V. 22, 23. The penetrance appears to be greater in the left-hand than in the right-hand part of the pedigree. (After Snyder)

both polydactylous, produced a family of 10 children, all affected, whereas if it were dominant there should be 3 affected : 1 normal. If the polydactyly in this family were strictly recessive, then I. 3, II. 5, III. 8, 18, 20, 21, IV. 1, 2, 8, 16, 19, 20, 21, 22, 26, 28, 32, V. 9, 21, 39, 40 (i.e., 21 persons) must all have been heterozygous for the gene, though normal. Of course this is possible, but it is a simpler assumption that the condition is one of variable dominance, requiring two doses for its expression in some families but frequently appearing (with low penetrance) when only one dose is present. Snyder is correct in assuming that if the abnormality is dominant it must be very imperfectly so. In another pedigree collected in the same community (Fig. 158) the condition would now be interpreted as one of dominance with low penetrance, three successive generations being skipped in two different lines. The alternative would be that twelve persons in this pedigree were carrying a single gene for polydactyly. This would

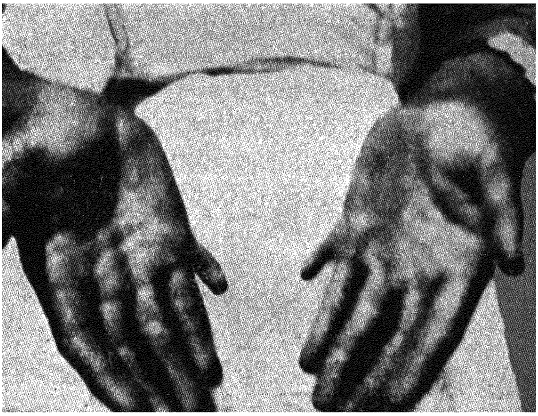


Fig. 157. Extra little finger in hands of a woman from Fig. 156. (After Snyder) (From the *J. of Heredity*)

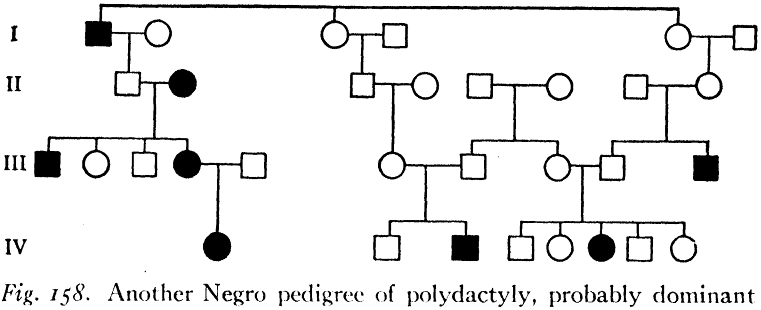


Fig. 158. Another Negro pedigree of polydactyly, probably dominant with low penetrance. (After Snyder)

mean that the recessive gene was very widespread in the population. *The higher the incidence of a recessive gene, the more difficult it is to distinguish from a dominant.* Conversely, it is difficult to show that a common gene with incomplete dominance is not really recessive. Incidentally it may be mentioned that Snyder blood-grouped the members of these families but found no evidence of linkage between the loci for blood group and polydactyly, so these genes are presumably in different chromosomes. Koehler (1929, 1930) also discussed these pedigrees and found them probably dominant.

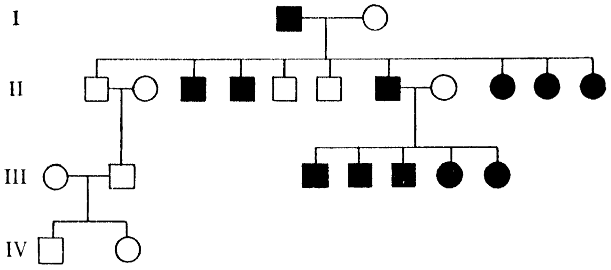


Fig. 159. Pedigree of polydactyly in whites. See text. (After Dehus and Snyder)

In a later paper (Dehus and Snyder, 1932) four new pedigrees of polydactyly, one in whites and three in negroes, are given with comments as to whether they are dominant or recessive. Unfortunately, no details of the nature of the abnormality are given, but presumably they represent ulnar hexadactyly of a relatively mild form. The first three appear to be dominant, with a total of 17 ♂ and 12 ♀ affected, sibships 26 affected : 14 normal. The white pedigree (Fig. 159) could be recessive only if I. 2 and II. 8 were both heterozygous. The fourth, a negro family with only three cases in three generations comprising 29 persons, appears clearly to be recessive, but if so, one wife must have been a carrier. It is not clear that polydactylism is more frequently recessive in negroes than in whites. Callan (1942) describes a Negro family in Texas with 29 cases (10 ♂ 14 ♀) in five generations, dominant but with three skips. The little finger is usually the extra, but in at least one it was the thumb. Some have extra toes as well. Many more pedigrees must be collected, with records of anatomical detail, before the relative frequency of the various dominant and recessive forms of polydactyly will be known.

In a family of Scandinavian ancestry in which the parents were first cousins and the two grandfathers were brothers, appeared three cases of polydactyly with eight normal sibs (Oliver, 1940). Each had an extra digit on each hand and foot at the base of the fifth digit. They were removed by surgery. These three were also feebleminded, they were slight in build and lacking in strength. The sixty blood relatives were all normal and it seems clear that a single recessive gene is involved.

That polydactyly and syndactyly are often associated has already been noted. McClintic (1935) has a dominant pedigree from Illinois with 15 cases (7♂ 8♀) in five generations, sibships 13 polydactyl : 12 normal. There were usually six digits on each hand and seven on each foot. In one case digits IV and V on each hand were webbed full length, the sixth digit being attached loosely at the base of the little finger; there were also two big toes (with two phalanges) on each foot; both feet also showed a reduced extra metatarsal belonging to the inner big toe. In one man the terminal phalanges on each thumb were doubled, these thumbs showing great strength. In five members the fingers or toes showed webbing. There was a large mortality among affected boys, so that only one reproduced, but there was no mental defect, blindness nor obesity.

Sewall Wright (1934, 1935) described an instructive case of polydactyly in the guinea pig. Normally the Caviidae have four toes on the front and three on their hind feet. An atavistic guinea pig appeared with vestiges of little toes, an extra left big toe, and vestigial "thumbs" on the fore feet. The mutation was semi-dominant. In crosses, 54 per cent had the thumb and little toe (on one or both sides), 20 per cent had thumbs only, 8 per cent had little toes only and 18 per cent were normal. When this stock was crossed to another which had little toes due to multiple factors, practically all the offspring had both thumbs and little toes. The heterozygotes were slightly heavier than normal, but the homozygotes generally died *in utero* at 10–15 mm. length, but occasionally survived to birth. They had short legs, paddle-like feet of double width with seven to twelve digits, a bulging forehead with occasional cerebral hernia. They were all microphthalmic and several had nasal clefts. Thus the gene which produced atavistic digits in the vigorous heterozygous pentadactyl condition is a lethal monster in the homozygous condition.

A polydactylous strain of mice (*M. musculus*) was described by Fortuyn (1939). They were highly inbred and showed polydactyly in 12 per cent of the males and 18 per cent of the females. This was the only abnormality. Polydactyls have an excess number of motor neurons enervating the foot, and in the spinal cord on the abnormal side. Generally only digit I of the right hind foot is more or less duplicated, but the left foot and other toes may be affected. Abnormal fathers transmit more often to their daughters than to their sons, but there is no genetic explanation of this.

Polydactyly in fowls is due to splitting of the first toe. It is frequently unilateral. Baumann and Landauer (1943) show that in such cases the motor cells in certain tracts of the anterior horn of the spinal cord are increased in number on the side of the extra toe. Sturkie (1943) shows that polydactyly can be suppressed in heterozygous chick embryos by a temperature only 1.5° C below normal. Hutt and Mueller (1943) find that it is also frequently suppressed in heterozygotes by inhibiting genes, and that polydactyly is linked with multiple spurs and duplex comb.

Syndactyly can occur in any degree, from cutaneous webbing to synostosis of the phalanges. The name of the gibbon, *Symphalangus syndactylus*, stresses its syndactyly. The webbing connects digits II and III. Webbing also occurs in the related genus Hylobates and in various marsupials and some other mammals (see Straus, 1926). The corresponding tendons are united for some distance. Schultz (1934) points out some twenty anatomical differences between the mountain gorilla (*G. beringei*) and the lowland species, *G. gorilla*, including syndactyly of the four toes in the former species. The anatomical significance of the various forms of syndactyly need not be further considered here, but it may be pointed out that webbing between all the toes is an early embryological condition in all the Primates. It persists longer between the second and third digits and is normally present in many adult marsupials, lemurs, some Old World monkeys and some gibbons.

Smith and Norwell (1894) described a boy of fifteen with digits III and IV of the right hand webbed to the tip, the nails joined, but with a terminal notch between them. The left was similar with minor differences. The feet had six toes, II and III being webbed in each foot nearly to the first joint, V and VI webbed up to the nail, the great toe very large and the fifth and sixth toes rotated downward (hammer-toe) so the nail was in contact with the ground, causing severe pain in walking. The father showed exactly the same condition, except that the big toes were abnormally small and there was no difficulty in walking. The pedigree of this family with both hands and feet affected included 21 cases (11 ♂ 10 ♀) in five generations. The condition was dominant with two skips, the sibships 20 affected : 6 normal.

Kemp and Ravn's family (1932) with 44 cases (26 ♂ 18 ♀) in six generations (sibships 43 affected : 44 normal) showed polydactyly and syndactyly with synostosis between the fourth and fifth metacarpals and a characteristic dislocation of the little finger. Syndactyly was present in twenty-nine, generally between the third and fourth fingers, but with variations in webbing and synostosis. Dislocation of the fifth finger was present in seventeen cases, and in eight cases polydactyly of the second digit, involving the two terminal phalanges or all three, with two nails present. Five others showed brachyphalangy of digit II. A similar triad of conditions was found in the toes. The malformations were generally symmetrical in both hands or feet and there was a characteristic delay in ossification of the hand bones. All these conditions must have been determined by a single gene, which was strictly dominant except for three skips. Probably many such mutations exist, having somewhat overlapping effects. There are probably a number of genes for syndactyly alone, producing slightly different effects as regards the degree or location of webbing or synostosis on fingers or toes. The inherited mutations affecting different parts of the skeleton of the hands and feet appear to be almost innumerable.

Webbing is most frequent between toes II and III. Weidenreich (1923) suggested the term *zygodactyly* for this condition, reserving the term *syndactyly* for cases of partial fusion or of synostosis (fusion of the bones). Hurlin (1920) described this condition in an old New England family, dominant, with five cases in three generations. Basler (1926) examined 476 boys and 652 girls in Tübingen and found 9 per cent of boys and 6.6 per cent of the girls with webbing between toes II and III. He distinguished between zyg. cutanea, when the toes are in actual contact, and zyg. membranacea when a web joins them. This web may be present in three degrees: (1) extending to the tip of the toes, (2) extending half way, (3) barely perceptible at the base. This frequency is much higher than that found (see Schultz, 1922) in the American army. Only eight cases, always between toes II and III, were found among 20,000 men. This probably included only the more marked cases.

LeGros Clark (1916) described a form of syndactyly which has some features of "split hand." Both hands of a girl of twenty lacked digits I, II and III, and digits IV and V were fused. The metacarpals IV and V were normal, but a metacarpal bone was lying crosswise between the heads of metacarpals III and IV. Her father and two brothers were in the same condition — hypodactyly combined with syndactyly.

Manson (1915, 1928) described a large family in which syndactyly and polydactyly appear together. It originated with one William Joseph, born in Aberystwyth about the beginning of the nineteenth century. He had webbing of the third and fourth fingers of both hands, and six toes on each foot, and was probably homozygous for this condition, since all his nine children had it (Fig. 160). There were 27 affected descendants (14♂ 13♀) to 21 normal sibs. Three of them had the abnormality complete in all limbs. Skiagraphs show that while there is considerable variation, the fourth digit of the hands and feet is consistently affected by partial or complete reduplication. This is an extremely rare condition. Nievergelt (1944b) records a Swiss family having a similar condition, with 9 cases (2 ♂ 7 ♀) in three generations, no skip. The hands showed a marked tendency towards duplication of digit IV, its basal phalanx being broad or double, in one hand with a Y-shaped metacarpal. There was also syndactyly as well as brachy-, campto- and clinodactyly in some fingers and an occasional partially or completely missing terminal phalanx (apical dystrophy).

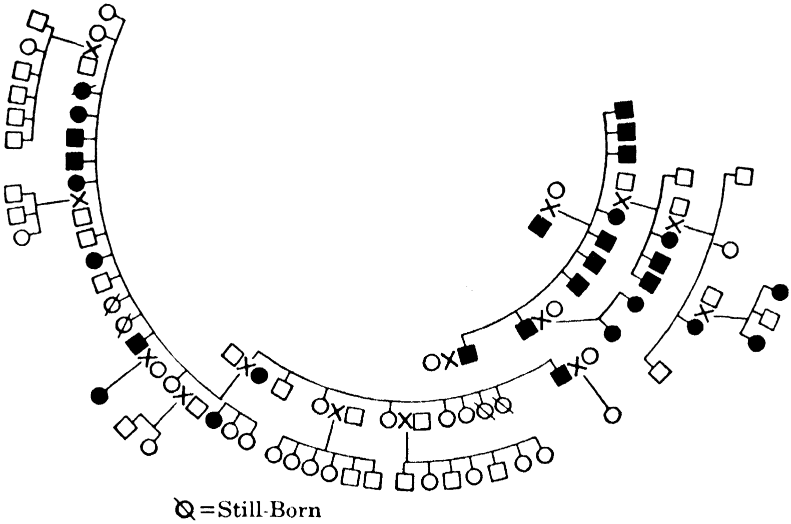


Fig. 160. Pedigree of dominant syndactyly and polydactyly. (After Manson)

Schofield (1922) described a case of webbed toes which occurred in fourteen male members of a family in four generations (Fig. 161).

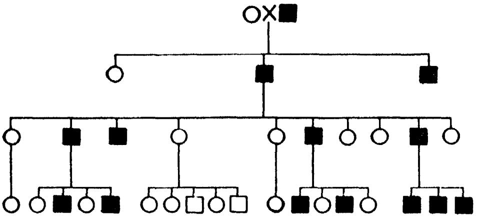
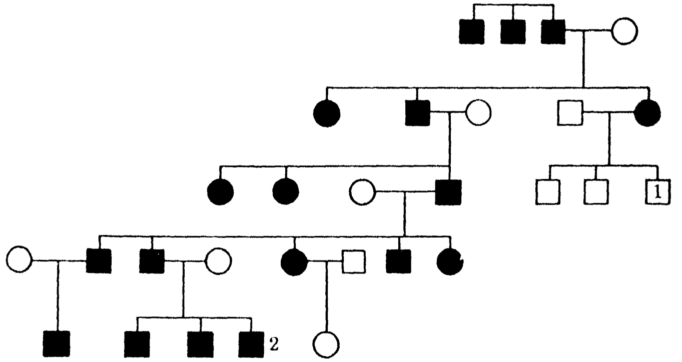


Fig. 161. Holandric inheritance of webbed toes. (After Schofield)

The web appears only between digits II and III, and is confined to the skin and flesh. It is always more marked in the right foot than the left, and is confined to the males, being transmitted only from father to son. It thus follows the course of the Y-chromosome. This has been generally accepted as a case of Y-linked inheritance, but some little doubt remains because of pedigrees in which only a few females have the character, but they do not transmit. Schultz (1922) cites Sommer's pedigree (Fig. 162) of webbing between II and III only in the right foot, 18 cases (12 ♂ 6 ♀) in five generations. The ratio of affected males to females is 2 : 1. This pedigree also indicates some sex-linkage, and it might be supposed that females do not transmit; but Wolff's (1921) pedigree (Fig. 163) of syndactyly, with 16 cases (11 ♂ 5 ♀) in three generations, which maintains the 2 : 1 ratio, shows transmission from a mother to her son. In this family, toes II and III on both feet were webbed nearly to the tip and the fingers, especially III and IV, were also webbed. This gene is probably an allele of that in Schofield's and Sommer's families. If so, they must all be inherited in the same way, i.e., as a dominant, with twice as many males as females affected. In Fantham's (1924) pedigree of a family of Scottish descent in South Africa (Fig. 164), the descent through males for two generations is followed by a family of thirteen, all



1 = Unknown number of sons, all normal
2 = Unknown number of sons, all webbed

Fig. 162. Pedigree of zygodactyly of right foot. (After Sommer)

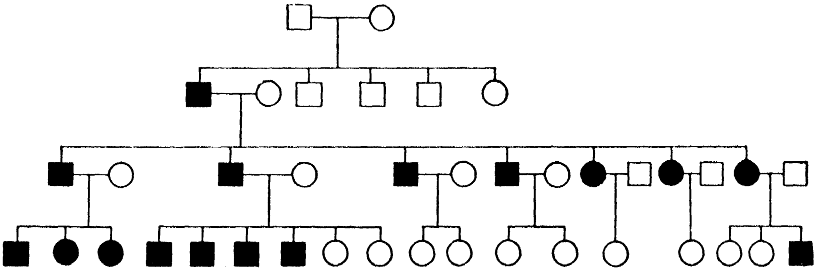


Fig. 163. Pedigree of syndactyly of certain fingers and toes. (After Wolff)

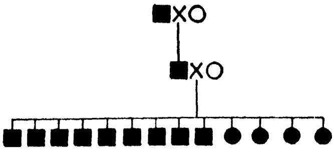


Fig. 164. Pedigree of syndactyly. (After Fantham)

syndactylous — a difficult circumstance to explain, for the father could not have been homozygous.

These and other pedigrees are compiled in Table 13. Plummer (1937) described an Irish family in South Dakota with webbing of the feet only, extending almost to the tips of *all* the toes. There were five cases (3♂ 2♀) in four generations (Fig. 165). It is probably a sex-linked dominant of low penetrance, as it passes from father to daughter and from the daughter to half her sons, but all the daughters should have it whereas two (II. 7 and IV. 5) do not. Lobster claw appears to be an extreme form of syndactyly (i.e., combined with ectrodactyly), but is probably genetically distinct and allelic. Cook (1935) described a Spanish family in which the mother and four of seven children were affected in hands or hands and feet. The mother had four fingers on each hand. She had seven normal sibs and may have been a mutation.

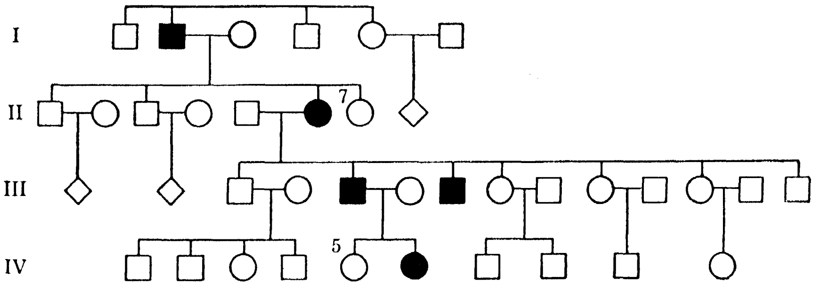


Fig. 165. Pedigree of webbed toes, probably sex-linked dominant of low penetrance. (After Plummer)

The genetics of syndactyly offers a problem of great interest. To solve it, the different genic types of syndactyly must be carefully distinguished. Probably the most frequent is the mild form, webbing of toes II and III. This is about twice as frequent in males as in females. In Newsholme's (1910) pedigree (Table 13), however, the sexes are equally affected and fingers III and IV may occasionally be webbed. In Table 13, the available pedigrees of syndactyly and related conditions have been analyzed, showing the number of affected and normal of each sex in the sibships.

In Schofield's (1922) pedigree the webbing is always longer on the right foot. It has often been cited as a case of inheritance in the Y-chromosome, since the fourteen syndactyls are all males. In comparison with the other pedigrees showing webbing of toes II and III, however, it appears that it may be only an extreme case. In Newsholme's pedigree there is a slight excess of affected females, but the eight pedigrees showing this type of syndactyly give a total of

TABLE 13

PEDIGREES OF SYNDACTYLY ANALYZED

Sibships			*Pedigrees of Syndactyly*				*Character*
			■	□	●	○	
Pfitzner	1898		9	2	5	2	Syndactyly with polydactyly
Newsholme	1910		10	2	12	0	Toes II & III (fingers III & IV in one male)
Sommer	1916		11 +	3 +	6	1	Not stated
Hurlin	1920		5	1	1	2	Toes II & III
Wolff	1921		11	3	5	11	Toes II & III (fingers III & IV)
Schofield	1922		14	0	0	11	Toes II & III
Wile	1922		2	1	3	2	Toes II & III
Castle	1923		0	4	4	3	Not stated
Fantham	1924		9	0	4	0	Toes II & III
Murphy	1925		7	11	7	4	Frequently all fingers & toes
Straus	1926	1	5	0	1	0	
		2	2	3	3	1	
		3	1	—	0	—	Mutation
		4	1	0	0	3	Recessive
		5	1	1	1	0	
Thomsen .	1927	I	28	6	11	15	Syndactyly & polydactyly
		II	5	7	10	3	Syndactyly & polydactyly
		III	11	6	3	8	Syndactyly & polydactyly
Bell	1931	1	4	7	4	6	Syndactyly & brachyphalangy
		2	7	7	9	5	Syndactyly
		3	2	2	2	3	Syndactyly & brachyphalangy
Dehus & Snyder	1932		4	7	4	5	Syndactyly with hexadactyly
Heston	1932	A	7	3	4	5	Toes II and III
		B	7	5	1	9	Toes II and III
Scott	1933		12	19	5	12	"Lobster-claw" type
Ströer	1935		7	17	10	1	Syndactyly & polydactyly
Wightman	1937		8	9	7	9	"Lobster claw"
Schade	1937	I	4	3	4	4	Syndactyly & polydactyly
		II	2	1	6	2	Syndactyly & polydactyly
Stiles & Weber	1938		5	1	12	1	Symphalangism
Bailey	1938		8	9	6	5	"Lobster-claw" type
			219	140	150	133	

65 affected males : 30 affected females, a 2 : 1 ratio in harmony with most of these pedigrees taken individually. The sex-ratio is not distorted, as the total males and females number 80 : 73. Hence one might conclude that a single dominant gene is responsible for webbing between toes II and III (and occasionally between fingers III and IV as well) but that for some unknown reason it generally expresses itself twice as frequently in males as females.

Murphy's pedigree, in which the webbing of fingers and toes is general, no doubt represents a different gene which is apparently a simple dominant. The family were of low mentality, living in an isolated mountain community. The eight pedigrees of syndactyly with polydactyly, presumably representing a third gene, give totals of 70 ♂ : 49 ♂ : 53 ♀ : 40 ♀, i.e., a large excess of affected over normal males and a smaller excess of affected over normal females. The eight pedigrees showing syndactyly of toes II and III give totals of 15 ♂ : 65 ♂ : 30 ♀ : 43 ♀, i.e., the percentage of affected is much lower both in males and females. This might be due to lack of ascertainment, as the character is often slight. The striking fact also appears that whereas in syndactyly with polydactyly 57 per cent of the affected are males, in syndactyly of toes II and III 66 per cent are females, notwithstanding that in Schofield's case all fourteen were males. It thus appears that all these pedigrees might be simple dominants. In two of the cases of "lobster claw" there is approximate equality of the four categories, suggesting simple dominance. In Scott's case there is again an excess of affected males and also of normal males, so that partial linkage with crossing-over between the X- and the Y-chromosome may be taking place. Differences of incidence in the two sexes can be understood in a condition like goitre, which has a physiological basis; but it is not easy to see why a developmental anatomical character such as syndactyly should find expression more easily in one sex than the other.

In Thomsen's large pedigree (Fig. 166) there is a large excess of affected males (31 ♂ : 11 ♀) and the sibships give 39 affected : 21 normal. In this pedigree, webbing is the main condition and polydactyly when present is in connection with the webbed fingers, so one gene only appears to be involved. The transmission is from father to son in 29 cases, father to daughter in 10, mother to son in 2 cases and mother to daughter in 1. Thus the father transmitted the gene in 39 cases and the mother in only 3. This difference must obviously be significant. The natural explanation is that the dominant gene is in the Y-chromosome, with a rather high rate of crossing-over to the X. If that is the case, a similar explanation will apply after all to Schofield's case (Fig. 161), where the gene remained in the Y, without any crossing-over, and, for example, to Wolff's case (Fig. 163). In the latter, II. 1 transmitted the condition to his four sons and three daughters. If the condition were an autosomal dominant, this would be unlikely, since he is presumably heterozygous, but if the gene were in the Y with crossing-over to the X in some of his germ cells this might well happen. The transmission from fathers is to nine sons and five daughters. It is then possible that the gene for syndactyly of toes II and III is an allele of that for syndactyly with polydactyly, both being present in the Y with a considerable frequency of crossing-over to the X.

In Heston's two pedigrees there are four skips, so the dominance is incomplete, but there is the usual excess of affected males. Bell's family 1 showed syndactyly of IV and V in each hand with bony fusion in the terminal phalanx only, the middle phalanx of the little finger being also very short. In family 2 the syndactyly is between fingers III and IV and toes II and III. Family 3 showed a short second phalanx in all the fingers with webbing of fingers II, III and IV. The big toes were broad and the second phalanges of all the toes were missing (brachydactyly). One boy also showed defects of ear and skull. In Wightman's family of lobster claw there is suppression of central digits and overgrowth of the marginal ones. In Bailey's family the hands vary from five digits with two webbed to a fusion into two groups of digits, two individuals having clubfoot and one having no feet. It may have arisen as a mutation. The symphalangism in Stiles and Weber's family consists in the absence of a joint between first and second phalanges in all the fingers, so that only the terminal phalanx can bend.

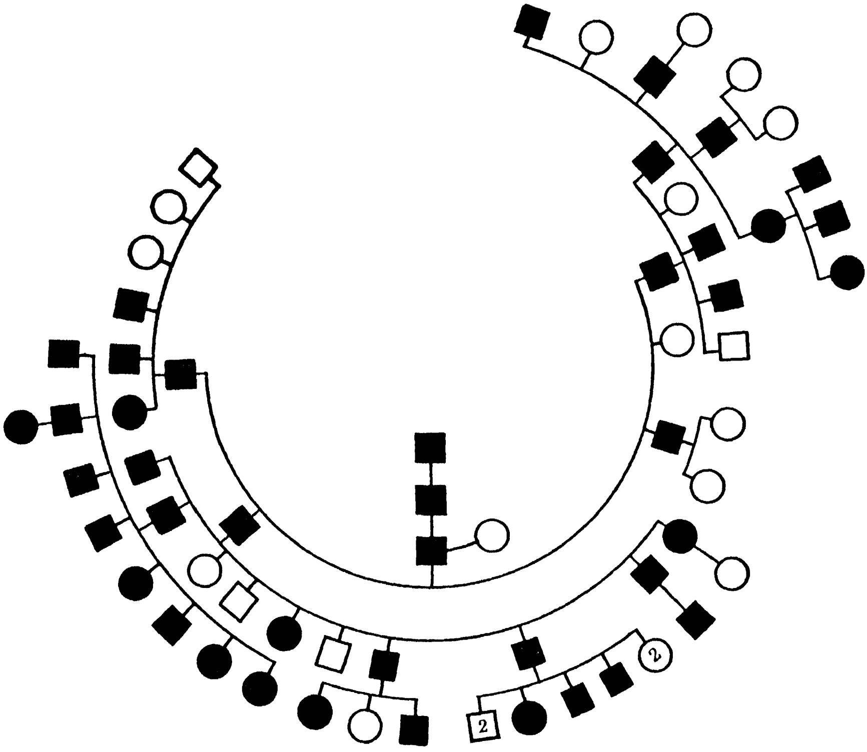


Fig. 166. Pedigree of polydactyly with syndactyly, probably in the Y-chromosome with crossing-over to the X. (After Thomsen)

Warkany and Nelson (1941) have shown that when rats are reared on a particular deficient diet their young show many abnormalities, including shortening or absence of tibia, fibula, radius, ulna and bones of hands and feet with syndactyly. There was also shortening of the mandible, fusion of ribs, and deformities of sternum, maxilla, clavicle and scapula. All these defects resulted from absence of one or more chemical substances from the food. Recent studies of Warkany and Schraffenberger (1944) indicate that this substance is riboflavin.

In a study of the finger-print patterns in cases of syndactyly (Grebe, 1940), the patterns were found to be symmetrical on the fused fingers or toes. The symmetry was generally determined by triradius formation on the side of the finger opposite the line of fusion, the fused fingers showing nearly mirror-image patterns. He believes that in cases of endogenous (inherited) syndactyly these symmetrical patterns are formed, while cases of exogenous origin can be distinguished because they show irregular changes in the whole pattern. Finger-print pattern apparently begins before the third month.

In 1587 Rueff described a case of the doubling of both hands and both feet. This condition has been very rare in the subsequent literature. Buettner (1938) described a girl whose left arm contained two ulnas and no radius. The hand had seven fingers, the order of the digits being 5, 4, 3, 2, 3, 4, 5, the middle finger being shortest and no thumbs present. This is *diplocheiry* or mirror-image doubling of the ulnar region of the hand. The mother had congenital luxation of the head of the radius in the right arm, the hand being small and the finger muscles atrophic. The distal end of the humerus was malformed in mother and child. These conditions were evidently genetically determined.

In *Madelung's deformity* the lower end of the ulna is prominent, there is bowing of the forearms and the hands are displaced ventrally. The main defect is dyschondroplasia of the lower radial epiphysis, the symptoms beginning at adolescence. Sloane (1943) describes the condition bilateral in two colored sisters. The survey of Anton, Reitz and Spiegel (1938) found 171 recorded cases, 75 per cent of them bilateral, the sex ratio about 4 ♀ : 1 ♂. The manner of inheritance is not yet clear.

Hawkes (1914) has compared different types of human foot as regards the *relative lengths of the first and second digits.* From an examination of the feet of 2300 persons, chiefly children, he finds the "L" type of foot, with the great toe longest and the other toes sloping back in an oblique line, the commonest. The "S" type, in which the second toe is longer than the great toe, is much less common. Not very rarely one foot will be of the L type, and one of the S type. This is in heterozygotes, but some persons with both feet L are heterozygous. The "E" type, in which digits I and II are of equal length, is very unusual. The L type of foot shows irregular dominance over the S type in inheritance, but the S type occurs more commonly in females than in males, and is commonest in the foetal stage. The male heterozygote tends to be L, and the female to be S, in foot pattern. Occasionally digit III is longer than digit II, and this condition was also found to be hereditary.

Clubbed Fingers and Toes

Hippocrates described clubbing of the fingers (Fig. 167) and toes as a clinical manifestation of intrathoracic disease. It has long been known to be associated with pulmonary or cardiac lesions, but may also occur as an inherited condition without other symptoms. Parkes-Weber (1919) described it in a man, his twin sons and a daughter; also in a man and his four sons and daughter. Kayne (1933) found drumstick fingers and a slight clubbing of the toes in a family born in Cyprus, the father and two sons being affected, two brothers and four sisters unaffected. The condition is sometimes called *Hippocratic nails.* Ebstein (1919, 1927) recorded two pedigrees: (1) a man and three sons, one of whom had a normal son who transmitted the condition to two of his sons; (2) three affected sons and three normal daughters. One of the sons had two sons (one affected). The latter had one affected son and one normal daughter. The condition is therefore an irregular dominant, much more frequent in the males. Ebstein (1919) also recorded three cases of *anonychia of the thumbs* in a family, and another family with *pollex bifidus.*

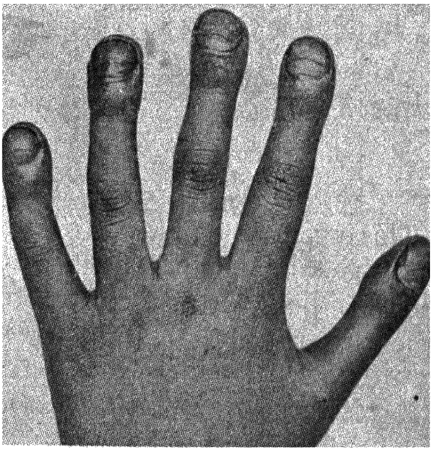


Fig. 167. Clubbed fingers in congenital morbus cordis. (After Tallerman)

Witherspoon (1936) cites many cases of clubbed fingers from the literature. X rays show spatulation of the bone in the terminal phalanges. The condition may be congenital or may appear gradually or quickly at a later date. An excessive volume of blood in the body has been suggested as a cause. In one family (six cases) the father and all the male offspring were affected, the four females normal. Neurath (1932) described four families in which clubbing of fingers and toes was inherited as a simple dominant. In a Hungarian family a man, his four children, his brother and paternal grandfather were affected.

Horsfall (1936) reported 20 cases (11 ♂ 9 ♀) of congenital familial *clubbing of the fingers and toes* in three families, including four generations in one family. The thumbs were always affected but some of the fingers might be unaffected. The condition is not rare and is not incompatible with a long and healthy life. Seaton (1938) described a family in Leeds in which the grandfather, father and two of three grandsons were affected. The fingers were like drumsticks, the nails livid and curved like an inverted watch-glass. X rays showed no change in the bones. In one, the enlargement began at twenty-one, in another the fingers had been clubbed as long as he could remember. The toes were similarly affected. There are many other familial cases in the literature.

Hammertoe is a distinct inherited condition. In one form the big toe may be deflected over the others. Gutmann (1925) gives a pedigree of unilateral hammertoe with 7 cases (3 ♂ 4 ♀) in four generations, dominant with one skip.

Heberden's Nodes

This name is applied to the enlargements of the terminal interphalangeal joints of the fingers, described by Heberden in 1802, under the term *digitorum nodi.* They are relatively common and it is agreed, following Charcot, that they are inherited and due to hypertrophic arthritis (Fig. 168). Duckworth (1889) described a family with Heberden's nodes in four generations, affecting mostly the female line but involving three brothers and a sister in one generation. There was no gout in the family. The nodes were formerly regarded as connected with gout. These nodes may occur idiopathically (inherited) or as a result of trauma. If only certain fingers are involved, the condition is probably of traumatic origin, but it often appears only a year or more after a finger injury. If many fingers are involved it is likely to be of the inherited type. Stecher (1940) has made an extended study of the condition, having examined nearly seven thousand adults in Cleveland and analyzed the incidence according to race, sex, age and occupation. Both the traumatic and inherited types tend to increase with age. The incidence of traumatic nodes is higher in men than women, in workmen than physicians, in white working people than Negroes.

Idiopathic nodes have a low incidence before sixty, then increase very rapidly in white women, much more slowly in men. The lower incidence in

Negroes appears to be a racial difference. Three degrees of the condition are recognized, in which the joint is, (1) enlarged, (2) enlarged and flexed, (3) enlarged, flexed and deviated. Several fingers are generally involved, but not the thumbs. Stecher published a number of pedigrees, but these were extreme cases selected because they demonstrated multiple cases in one family. In only three families could transmission be through the father. In one case the father's mother was affected; in two cases the paternal aunt. In an analysis of 68 families, 67 mothers were affected, but only 33 of the 129 sisters. Because of the late onset the numbers are difficult to evaluate. Three-quarters of the cases had their onset by fifty-three, and seven-eighths by fifty-nine years of age.

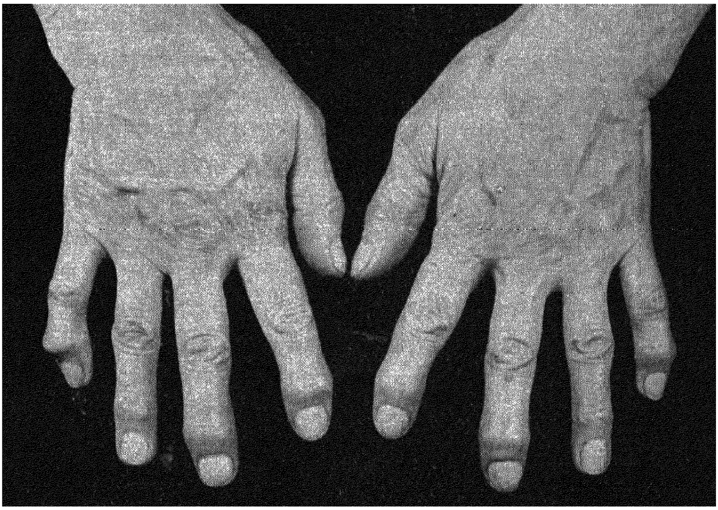


Fig. 168. Heberden's nodes. (Photograph from Dr. R. M. Stecher)

Three families are given in pedigree form (Stecher, 1941): (1) a mother and four daughters affected, three sons and a daughter normal; (2) parents normal, seven daughters affected, two sons and one daughter unaffected; (3) father's sister, four daughters and one son affected, one daughter (aged thirty-eight) unaffected. There is probably a single gene involved. Stecher and Hersh[1] find that the gene is dominant in females and recessive in males. In the general population, 2.7 per cent are homozygous for this gene, 27.2 per cent heterozygous. The mothers of affected persons are affected twice as frequently and the sisters three times as frequently as the general population. The old belief that these enlargements resulted from hard work or from "having the hands in water" is fallacious. They occur in leisured women as well as scrub women.

In a further paper, Stecher and Hersh (1944) have analyzed the inheritance of Heberden's nodes in 74 families. They find the idiopathic form not only ten times as frequent in women as men (30 per cent of women and 3 per cent of men affected), but that the autosomal gene, D, is dominant in females and recessive in males. It thus resembles baldness genetically, except that the latter is recessive in females and dominant in males. It is to be hoped that many similar studies of gene frequencies will be made.

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[1] *Records Genet. Soc. Amer.* 1943, No. 12, p. 55.

Bilateral congenital *fusion of the capitate and hamate bones* in the wrist is a rare condition reported by White (1944). Apparently no case was recorded before 1932. Mahaffy (1945) records a rare case of bilateral *fusion of the calcaneum and cuboid* in a man. He found only two previous cases on record. He also found two cases of *talonavicular synostosis* reported. Such cases are probably all inherited as irregular dominants. Henry (1945) records a case of fusion of the scaphoid (navicular) and greater multangular (trapezium) bones in a soldier. He cites other cases of bilateral fusion of carpal bones from the literature and suggests that such fusions occur between bones which ossify at the same period.

Pryor (1907) studied the *order of ossification of the eight carpal bones* in 10 families of children, based on 360 skiagraphs of children generally under seven years of age. The order was symmetrical in both hands but varied in different families. He concluded that differences in order of ossification were inherited. In a later study (1939), he applied the method to multiple births. He confirmed that the Kerner triplets were MZ by showing the same order of ossification of the carpal bones. In the Schense quadruplets the ossification order tends to confirm that they are 2 + 1 + 1, i.e., derived from three egg cells. In the Morlok quadruplets, all eight hands show the same sequence and there is an extra epiphysis at the end of the second metacarpal in all eight hands. The conclusion is clear that variations in the sequence of carpal ossification are genetically determined. Pryor (1936) found that six years and one month was the best age for determining the order of carpal ossification. The gene complex determines the entire pattern in which the carpal bones are laid down, first in cartilage and then in bone. X rays of these bones in the Perricone male quadruplets confirms that they are a four-egg set although all of the same sex. This condition must be extremely rare. In A there were four centres of ossification in each hand and the metacarpals and phalanges were much shorter than in the other three. B at the same age had four ossification centres in the right hand and five in the left and they were in a different sequence. C had only three centres in each carpus, and D had six in the right and seven in the left.

Veit (1939) described a malformation involving both hands and arms. The arms were short, their stumps bearing three small fingers, in a woman and her granddaughter, the father having epilepsy, debility, and left pes equinovarus (clubfoot). The daughter and two of *her* daughters by a normal man had asymmetrical malformations of both hands, anomalies in the position of radius and ulna, stiff elbow joints, deformed wrist, no thumbs, and psychic debility. Several members of the family had oligodactyly, thumbs with three phalanges and other defects. Four families with similar conditions have been previously described. Stiles and Dougan (1940) describe a family descended from a man who had crooked little fingers, wrists slightly bent and radio-ulnar synostosis. In the two succeeding generations, twelve of twenty-six descendants showed malformations, some of the fingers, some of fingers and wrists, some of fingers, wrists, arms and shoulders. The extreme condition is *fin-like short arms with three fingers attached*. The inheritance is dominant, with one skip. Brown (1943) records a single case — probably a mutation — a man with three-fingered hands attached just below the elbow, with bilateral anomalies of the ribs, clavicles and scapulae.

Radio-ulnar synostosis is not very rare. It results from imperfect separation by mesenchymatous tissue of the cartilaginous axials of the forearm. In the Sirenia the radius and ulna are fused at both ends, in the Proboscidea they are permanently crossed, in Hyrax they are often ankylosed, and in certain Insectivora they are fused distally. In some animal groups a mutation producing ankylosis would be advantageous and they were probably developed further by natural selection. Davenport, Taylor and Nelson (1924) made an extensive study of radio-ulnar synostosis, congenital pronation or inability to hold the hand with palm upward. In 1912, thirty-eight cases of this rare condition were listed and as many more were noted in the next twelve years. It is bilateral in about half the cases and is not to be ascribed to intra-uterine injury, external repression or inflammatory disease producing secondary ankylosis. Davenport *et al.* described fifteen families. The main part of the M. pedigree (Russian Jews from Minsk) is given in Fig. 7, p. 14. The 13 cases (12 ♂ 1 ♀) in three generations show clear dominance, the sibships numbering 12 affected : 13 normal. Every individual was bilaterally affected. The single affected female suggests that the defect may be in the Y-chromosome with an occasional cross-over to the X. Probably crossing-over occurred in certain germ cells of III. 7, since he had a normal son as well as an affected daughter. In some other pedigrees there is an excess of affected males, but the inheritance is irregularly dominant. In certain families it may be recessive, and there are several single cases with normal ancestry. Probably several different biotypes exist, and the condition shows considerable variation. Abbott's (1892) case had 5♂ 2♀ in four generations, with three skips. In some strains the condition is mostly or wholly unilateral, and there is an excess of normal females. Davenport suggests that in some pedigrees two genes are present, **AaBb** being synostotic while **aaBb** is not. These seem more likely to be cases of lower penetrance.

Sireniform malformations of the posterior limbs bear some similarity. The condition is rare in man. Ask-Upmark (1936) found 166 cases described up to 1927. The body is normal but the lower limbs are replaced by a structure like a fish-tail with two parts at the end corresponding to feet, two femurs, one bone only in the part corresponding to the lower leg. There are no bones in the "feet," no muscles below the knees, and a single artery. The central factor in the sireniform malformation appears to be the abnormal development of the cells of the trunk-tail node. Kampmeier (1927), in describing another case, found 166 recorded. It occurs in various degrees and is frequently associated with anterior abnormalities such as harelip and syndactyly. The 52 cases in which sex was determined were 38♂ 14♀. The first case in any mammal is recorded by Gluecksohn-Schoenheimer and Dunn (1945) in mice carrying various alleles of the T (tailless) gene (see p. 504). Five sirens appeared, of at least three different types. The posterior internal organs were also missing and there were other abnormalities. The same stocks of mice produced six cases with various degrees of otocephaly (aprosopi) and eleven cases in which there were large intestinal gaps, probably from hernia with subsequent loss. The T locus probably includes a chromosome inversion, and it is possible that this condition leads to further defects through chromosome deficiencies and duplications. Töndury (1944) describes the anatomy of three infants of related type in which the posterior end of the body was more or less sirenoid.

Stockard (1936, 1941), from his extensive experiments in crossing dogs, concluded that the big breeds such as St. Bernard probably have three dominant genes, **AMP**, which, when all present, paralyze the thigh muscles. In crosses between St. Bernards and Great Danes, almost all the F_1 and about one-third of the F_2 had posterior paralysis. If one breed was **AMp** and the other **amP**, the three genes being in different chromosomes, then the F_2 would show 27 paralyzed in 64. In the presence of these three factors the death of certain sympathetic neurones (the motor and preganglionic) in the lateral and anterior horns of the spinal cord in the lumbar region takes place eight to fourteen weeks after birth. These genes exert a lethal effect on certain nerve cells. Stockard makes the reasonable suggestion that similar mutations in certain coastal Carnivora may have produced the Pinnipedia (seals, walrus, elephant-seals), beginning with a mutation like that found in these breeds of dogs. The rare hereditary form of paralysis in very young children, known as the Werdnig-Hoffmann paralysis, is similarly due to spinal nuclear atrophy and was reported nearly fifty years ago. But in children, although it tends to begin in the thigh, it spreads throughout the spinal cord.

The Newfoundland dogs and Dachshunds have webbed toes, which may be associated with achondroplasia or pituitary disturbance. The sireniform malformation in man is then probably the result of a single mutation in the germplasm. Whether it is dominant or recessive cannot be determined because such individuals never survive, but evidence could be obtained by determining the incidence of consanguinity between the parents in such cases. Frädrich (1936) described three sireniform human foetuses.

Davies (1930) described two cases of radio-ulnar synostosis without evidence of an hereditary origin. Such cases may be mutations. McFarland (1930) saw at least ten cases and recent records of at least six more (three bilateral). Dislocation of the head of the radius is the original condition, followed by fusion of the proximal ends of radius and ulna. Thomas (1926) records a family under the name of radio-ulnar olisthy. There were 7 cases (4 ♂ 3 ♀) in four generations, inheritance strictly dominant. *Synostosis of humerus and radius* is described by Roth (1926) in a family with three of five children of normal parents affected. In the second child both elbows were fixed at 90°, in the third at 80° and in the fifth at 70°. This condition appears to be recessive.

Another crippling deformity arose as a mutation (Hegdekatti, 1939) from normal parents in a Hindu community in Bombay in which marriage is restricted to members of one sect. On the hands, all the fingers are missing except the little finger (*monodactyly*). This does not taper, is generally flexed at the tip and the nail is abnormal. Some hands have metacarpal bones, others are like a thick pad, with friction-skin patterns quite different from the normal. The feet have one rudimentary toe with a rudiment of nail and a *lateral outgrowth below the ankle joint*, which makes walking difficult. The condition is more uniform than many such malformations. It is strictly dominant, with 23 affected and 23 normal descendants in six generations.

A recessive condition in which broad, fleshy hands and short fingers are associated with a form of dwarfing resembling achondroplasia, was recorded in three of six children of normal parents by Drysdale and Herringham (1908). The head was large, the forehead prominent, the nose flattened, base not depressed. The finger pulp extends beyond the nails, which are raised, and the feet show similar changes.

Apical Dystrophy

This condition was formerly confused with other forms of finger-shortening, but has been clearly distinguished by MacArthur and McCullough (1932). They described a family in Toronto with fifteen cases in three generations, strictly dominant. It is an unusual form of shortened fingers (and to a less extent toes) manifested by absence of the terminal portions of fingers II to V and nearly or quite complete absence of nails (Fig. 169). The thumbs are not shortened, but are abnormally broad and flat and show a tendency to doubling of the nail. The fingers resemble the stumps left after amputation of the terminal third, half or two-thirds. They look like the hands depicted on the walls of Paleolithic caves in the Pyrenees, which are supposed to be the result of mutilation. Even in one hand, stages of hypophalangy with tri-, bi- and nearly monophalangic digits may be seen. Usually most of the mid phalanx and sometimes the base of the third is present. Figure 170 shows the osteological teratology. Some affected members have syndactyly of fingers III and IV and of some toes.

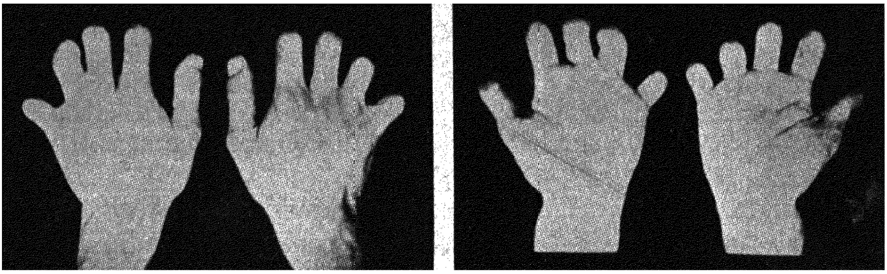

Fig. 169. Hands showing apical dystrophy. (After MacArthur and McCullough)

When the embryo is about 20 mm. in length in the second foetal month, certain fingers and toes are connected by webs, the fingers and outer toes are about to develop their terminal portions and the thumb is differentiating its terminal phalanx. The gene is pictured as an inhibiting influence, producing a partial arrest of development at this brief period. In brachyphalangy, on the other hand, precocious closing of the line between the epiphysis and the phalanx stops elongation of the phalanx after birth.

The authors point out that Cragg and Drinkwater's (1916) case, with 27 affected (10♂ 17♀) in five generations, is also apical dystrophy. The same deficiency was described at Uxbridge in a mother and two children, by Dr. Kellie (1808). This was said to have been inherited for ten generations and only through the mothers, but the latter statement at least is subject to doubt. Exactly the same conditions were seen in a family in six generations by Mackinder (1857). Drey's (1912) family, with 9 cases (4♂ 5♀) in three generations, is an allied condition, but the shortening was mainly in digits III and IV. Synostosis of the phalanges of the index finger, also present, would be due to a separate gene.

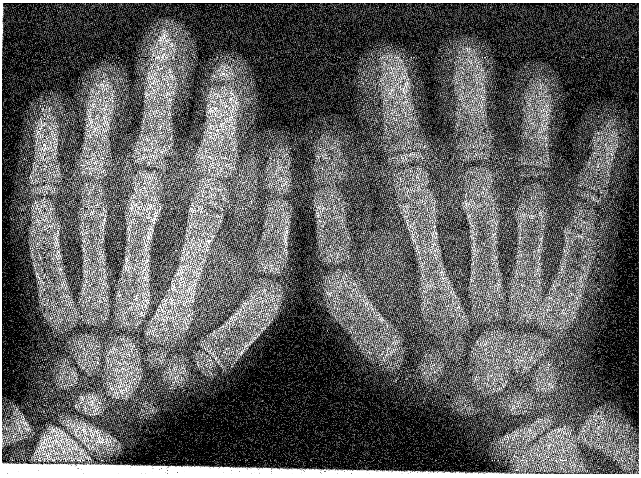

Fig. 170. Skiagraph showing the hand bones in apical dystrophy. (After MacArthur and McCullough)

MacArthur and McCullough proposed a classification of digital abnormalities, which can be adopted in essentials as follows:

1. Shortening prenatal, involving digits II–V (apical dystrophy).
2. Shortening not fully apparent at birth; precocious ossification of certain rows of epiphyses (brachyphalangy in wide sense).
   A. Metacarpals (or -tarsals) only affected. Brachymetapody.
   B. Middle phalanges only affected. Brachymesophalangy.
      1. More widespread shortening, including the long bones.
         a. Reduction marked, phalanges absent or short and fused to the terminal phalanx. Hypophalangy, brachydactyly, biphalangy.
         b. Reduction less marked, mid-phalanges not ankylosed to terminal. Minor brachydactyly.
      2. Shortening restricted to mid-phalanx of certain digits, especially V and II; stature normal.
         a. Digits III–V (toes only) without mid-phalanx.
         b. Digits II of hands and feet, mid-phalanx showing (1) marked (2) slight, reduction.
         c. Digits V, II or IV of hand showing slight asymmetrical shortening on mesial side. Clinodactyly.
   C. Terminal phalanges shortened. Brachytelophalangy.
      1. Shortening confined to thumbs, which are broad and clubbed. Brachymegalodactyly.

These various conditions appear to be represented by a series of genes, which are quite likely alleles, differing in the strength and time of their action.

Morvan's syndrome is a rare condition, described in 1883, in which the nails are abnormal and the terminal phalanges may show a condition like apical dystrophy. Parks and Staples (1945) describe two cases, in one of which the parents were first cousins. They found only seven other cases recorded, two of them in brother and sister. Some cases have painless foot ulcers, but syringomyelia (cavities in the spinal cord) is not always involved.

Carpal displacement (Ellsworth, 1927) in a family with five cases (all females) in four generations, is probably a simple dominant. The carpus is displaced forwards on the radius and ulna and the wrist articulations are deformed.

Congenital flatfoot is an arrest of development, since man is the only primate having a longitudinal arch. According to Kuhns (1942) some 50 per cent of children show foot weakness when they begin to walk. A small number, about 0.5 per cent, show persistent ligamentous relaxation of the feet with displacement of the medial tarsal bones on walking. Such feet show a tendency to go into calcaneovalgus (see p. 390). The foot relaxation is regarded by Kuhns as a part of the generalized relaxation of ligaments and subcutaneous tissue in the Ehlers-Danlos syndrome. He believes the tendency to flatfoot to be inherited as a recessive trait.

Hyperextensibility or doublejointedness of the thumbs may occur in the first joint or the second. The condition appears to be usually an irregular dominant rather than recessive. Key (1927) described a family in which the father and four sons but none of the five daughters were affected. The mobility extended to all the finger joints and the wrists. The father's parents, his nine brothers and one sister were normal, so it probably arose *de novo* with him, and inheritance in the Y-chromosome is indicated but not proven. Hypermobility, whether in one joint or many, is ascribed to extensibility of the ligaments. Whitney (1932) described a family with 13 cases (5 ♂ 6 ♀) in three generations, in which the second joint showed hypermobility. He cited several other small families and found 5 to 10 per cent of people affected in small groups tested.

Hyperextensibility of the metacarpo-phalangeal joints is also inherited. Schlaginhaufen (1934) published a pedigree in which the fingers are "double-jointed" at the base. The condition is probably not uncommon. It occurs in different degrees and is more marked in children than adults. This family contains 7 cases (2 ♂ 5 ♀) in two generations, with 10 others showing lesser degrees of stretchability. The pedigree suggests irregular dominance, with variable expressivity and incomplete penetrance. A pedigree of Hanhart contains twenty cases. In Sturkie's (1941) family all the finger joints are hyperextensible. The 9 descendants (3♂ 6♀) in two generations from one woman have all inherited her peculiarity. In an ordinary dominant, half should have been normal. The knees, elbows and toes were also affected in some. In a second family the condition was less extreme. A woman with normal parents and four normal sisters transmitted the condition to a daughter and grandson while a son (and his two sons) was normal.

Luxation of the head of the radius is frequently associated with other congenital malformations of the elbow joint. Abbott (1892) described 7 cases (5♂ 2♀) in a family in four generations. In four cases the effect was bilateral. Dislocation of the radius was almost directly forwards and was noticed when the child began to use its hands. The inheritance was irregularly dominant with three skips.

Bonneberg in 1893 collected thirty cases of *luxatio radii*, twelve of them bilateral. The luxation can be forward or backward. Trauner and Rieger (1925) cite a family with six cases in four generations, dominant. There were related anomalies of the finger and knee joints, and the nails of the thumb and first finger ended in a ragged malformed outer tip.

The familial occurrence of *osteochondritis dissecans* (inflammation of cartilage resulting in splitting off pieces into the joint) shows that there are local defects in the cartilage of the whole elbow region, which are of endogenous origin. Congenital luxations, according to Pfeiffer (1938) are preceded by a primary distortion of growth and development. Subluxation and intermediate conditions also exist. A case is cited, in which the mother had radius luxation in both arms, and both femurs dislocated. One child had luxation of both radius and ulna, another had luxation of both femurs and the radius and ulna on both sides. In cases of ulnar luxation there is aplasia of the distal end of the humerus.

A different *malformation of the elbow joint* was described by Herzog (1927) in a woman, her sister, father and paternal grandmother. It was bilateral in every case and consisted in the separation of the broad fossa olecrani into a lateral and a deep medial recess, the olecranon being small and slightly arched. The mechanism of movement was abnormal. The inheritance is evidently dominant.

In a legal case (Nievergelt 1944a) a man had *multiple malformations* of the limbs, viz. elbow joint dysplasia, bilateral radio-ulnar synostosis, misshapen lower leg bones, bilateral club foot (pes varus) with synostoses of the tarsal bones, metatarsals and toes. He had an illegitimate son showing essentially the same malformations, by each of three different women. The condition was therefore strongly dominant. In another family five members showed different degrees of a bilateral *malformation of the hands.*

Luxatio coxae, or congenital dislocation of the hip, is also inherited. Roch (1925) was the first to collect a large material on its inheritance from the clinics of Tübingen and Leipzig. He cites 189 cases in 29 pedigrees. The condition has been known from the time of Hippocrates. Roch finds it 5.5 times as frequent in women as men. The pedigrees as they stand indicate recessive inheritance. He regarded it as a sign of degeneration, more frequent in families whose ancestors contained drinkers and epileptics. Bryn (1926) finds that the condition is very frequent in the hybrid population of Finmark, compared with other parts of Scandinavia. According to him, it has been repeatedly shown to be very much more frequent in hybrid than in pure races. In Lapp × Norwegian, the small pelvis and narrow acetabulum of the Lapp woman, combined with the large caput femoris of the Norwegian, makes luxation easy, and may be regarded as a disharmony arising from this cross.

Hooff (1928) found 932 cases (132 ♂ 800 ♀) among 14,320 examined in ten years at the orthopaedic hospital in Munich. It was thus six times as frequent in females as in males, and 20 per cent of the cases were familial. The 112 pedigrees (see Fig. 171) mostly require the same explanation as those of Roth, except one with direct descent through four generations and two or three others which appear to be irregular dominants. In a pair of twins very probably identical, only one of them had it, showing incomplete penetrance. The greater frequency of luxation in female children is due to the difference in shape of the pelvis, although in newborn children there is a difference

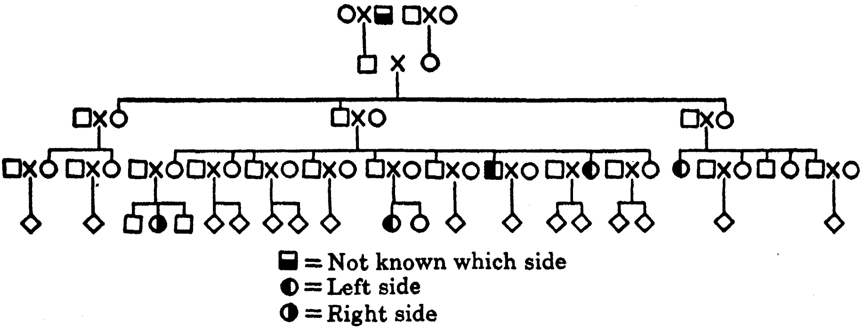

Fig. 171. Inheritance of luxatio coxae. (After Hooff)

of less than one degree in the angle the femur makes with the horizontal in the two sexes. But during the first year the differences increase. Luxation is significantly more frequent in the left than the right femur, especially in the female sex, but there is no known reason why this should be so. Frequently (in 42 per cent of cases) both femurs are dislocated. Hayashi and Matsuoka found luxation relatively common in Tokyo. This is ascribed to the fact that the Japanese are compounded of Mongolian, Ainu and other (Malayan) elements. Luxation is also known to occur in North Africa, Sudan, Madagascar, and Annam; whereas among the Chinese of Shanghai, who are regarded as a relatively pure race, it is said to be almost nonexistent, only three cases occurring in twenty years in a hospital clinic seeing 70,000 patients annually. There are also great differences in its frequency in parts of Germany and the Tyrol.

In his breeding experiments with mice, Rabaud (1919) describes the appearance of a race from wild × albino, in which the tibia is replaced more or less completely by a fibrous tract, while the fibula is heavy and incurved. As a result, the leg is bent on the thigh and will not support the animal. It walks on the distal end of the femur, which thus appears dislocated. This condition only appeared in the descendants of one pair from the original cross. When crossed with normal it was recessive, usually giving a 3 : 1 ratio. Two abnormals crossed together afterwards gave 18 normal : 74 abnormal, 9 of them luxated on one side only. Extracted normals crossed together gave 3 : 1, and normal × luxated gave 1 : 1. In man the penetrance is lower.

The so-called congenital dislocation generally develops in the first two years after birth, sometimes later. Faber (1938), by use of X rays, found deficiency in ossification of cartilage as the cause in every case. He studied 19 families, with 150 persons in one pedigree. In all families, where only one member had hip dislocation he found several with deficient ossification. On this basis he concludes that the condition is a simple irregular dominant, four times as frequent as it was previously considered. Taking into consideration all kinds of disturbance of development in the area of the hip joint, he finds no great difference in incidence in the sexes, but actual dislocation is more frequent in the female. The congenital maldevelopment is in the iliac segment of the bony acetabular rim. This defective ossification results in a "flat" acetabulum, which is the inherited condition. Environmental factors determine whether dislocation will follow. When it has occurred, secondary changes lead to the thickening of the articular cartilage unless the femur head is replaced. Badgley (1943) finds that the primary embryological abnormality is failure of rotation of the limb bud and Strayer (1943) thinks the foetal position is involved. Hart (1942) agrees that dislocation results from *flat socket* or hip dysplasia, due to a dominant gene.

Absence of head of femur is a closely related condition. Tucker (1934) described a family in which six members in four generations were cripples from this cause. It was dominant with one skip. Five other members had fragilitas ossium. Pfeiffer (1937) shows, from a study of seventeen unilateral and three bilateral cases, that femur and pelvis defect is evidently involved in all cases of congenital luxation. The pelvic bones show different forms of under-development and change in shape. In some cases the defect is mainly in the head of the femur, in others in the pelvis, the acetabulum being frequently shallow or defective.

The inheritance of the *supracondyloid process* of the humerus was shown by Struthers (1873) in a family (Fig. 172). This process or hook is a vestigial character which can be felt in the living person. It was on the left side in the father and three sons, bilateral in one, who also showed it more strongly in the left arm. Struthers suggested that the frequency in the population might be 1 in 50. The idea that this process might be more frequent in mental defectives or insane proves to be without foundation (Terry and Cady, 1923; Cady and Francis, 1927), its frequency among 2665 inmates of institutions being about 1.5 per cent. On the skeleton it may be found as a rough-trace, ridge, tubercle or process. Including these traces, Hrdlička (1923) found it in 63.8 per cent of whites and Terry in 34.6 per cent of Negroes, but the only Negro who had small bilateral spurs showed evidence of white ancestry. Terry (1930) found that while the complete process occurs in about 1 per cent of whites, it was rarely if ever recorded in pure Negroes or Indians, the incidence of all stages being much lower. Hrdlička found the full process in 3 Indian humeri out of 3094 examined, and in 2 out of 128 Eskimo humeri. Its incidence in Mongolians is also low and it has not been found in Melanesians or Australian aborigines. It thus appears to be rare or absent in primitive man, anthropoids and many of the lower apes, while experiencing a recrudescence in whites and Eskimos.

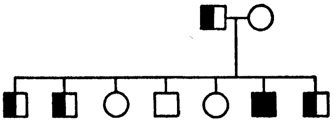

Fig. 172. Inheritance of the supracondyloid process. (After Struthers)

Acheiropodia, or absence of hands and feet, is a very rare abnormality. Peacock (1929) gives an account of a unique family in Brazil, with two photographs. According to the information given in the third and fullest account, a man married his niece. Of their 12 children, 6 were affected (4♂ 2♀) and there were 4 normal daughters, 2 of whom married and had 9 healthy children. The condition appears to be recessive. In those affected, the forearms are represented by an osseous appendage 4 cm. long with a nail at the tip; the lower legs by about two-thirds of the tibia, without muscles attached. The patella is present. One of the affected men was a cretin and another was mentally deficient. These cripples could feed themselves and do light work. Several members showed tardy pupillary reflexes, indicating syphilis. The birth order of those affected was the first, fifth, sixth, eighth, tenth, and twelfth child. Koehler (1936) gives another account of the family. Two other families are cited each with three cases of *acheiria* (one hand missing) in three generations, apparently irregular dominant. In a fourth family a woman with normal parents and sibs had arm stumps about 9 in. long, one with a thumb, the other a little finger. The thighs had small feet with two and four toes respectively attached to them — the condition thus approaching phocomelia. Adams and Oliver (1945) describe a condition closely similar to acheiropodia but less extreme. In marked cases the hands and lower legs were missing, in some limbs only the phalanges and certain metacarpals were absent while other limbs were normal. Two also had a defect in the vertex of scalp and skull. There were eight cases in three generations of a family, inheritance dominant. Regnault (1911) described a dog, twelve years old, with no forelegs. He tried amputating the forelegs of mice for several generations, with no effect! Johnson (1940) described complete absence of legs in pigs as a simple recessive condition.

Various cases of absence of the fibula have been described. Dankmeijer (1935) described the anatomy in a case of *absence of the tibia* and found 77 cases published since 1861, 21 of which were bilateral. This defect was in 35 males and 22 females; 32 were on the right and only 6 on the left leg. Ollerenshaw (1925) described a case of absence of the tibia, associated with many changes in the leg muscles. He regarded congenital defect of the long bones as due to interference with growth of the limb buds in the first few weeks of the foetus. In modern embryological terms, the evocator for a particular structure has failed at the critical period. Other abnormalities are generally associated and Dankmeijer concludes that the disturbance in development was at or before differentiation of the tibia from the blastema. As all the cases appear to be single, there is no evidence of the manner of inheritance.

Considerable light has been thrown on these abnormalities of the limbs by experimental work with mice. Bagg (1929) studied the descendants of X-rayed mice in which there was a high percentage of congenital limb defects, syndactyly, clubfeet, hypodactyly, polydactyly and "amputation." In two thousand control mice they failed to appear. There was also associated blindness, and occasional absence of one or both kidneys and absence of testis and liver. The inherited defects began to appear in the third generation from the X-rayed animals. Among 5280 mice, 291 had clubfoot. The left foot was affected more than twice as frequently as the right, and the left hind foot most frequently of all, but there was no difference in sex incidence. Clubbing was frequently associated with syndactyly, hypodactyly was recorded in 27 animals, amputation in 16; polydactyly occurred only in the hind limbs and generally on the right side, the big toe generally being reduplicated.

Examined *in utero*, it was found that the earliest foot defect was associated with a bleb, which raises the epithelium in a local area. Bleb formation was considered to be due to an hereditary anomaly of the lymph vessels, and it acted as a mechanical hindrance. Blood later escaped into the bleb, forming a clot which may persist until birth. The extent of this pathological process determines whether the foot will show congenital amputation, clubbing, hypodactyly or syndactyly. These abnormalities are recessive to normal in inheritance and they approach the Mendelian expectation when considered as the manifestation of one general tendency. Polydactyly was regarded as the result of arrest of development in the early primordia of toes, some reduplications of rudiments occurring on recovery. Bean (1929) found at least seventeen types of abnormality, from slight to gross, in these mice. Fusion of tarsal or carpal bones occurred in practically all cases, including some which were otherwise normal.

Bonnevie (1934) made an embryological study of the bleb formation in these embryo mice. The blebs form on the dorsal side of the head and body, minute blebs forming on the hind legs. The bleb fluid is normally expelled through an opening in the roof of the embryological myelencephalon, but the quantity expelled is excessive and its mere pressure hinders the development, producing the abnormalities as secondary effects. Crosses showed, however, that modifying factors influence the localization of these abnormalities. The main gene causes abnormal increase in cerebrospinal fluid in embryos 7 mm. long and its expulsion through the foramen anterius in the myelencephalon, whence it surrounds the embryonic eyes, producing abnormalities of the cornea and eyelids. Another bleb may form in a concavity across the shoulders and in other parts. Many blebs are absorbed, leaving no trace. The "penetrance" of the gene for different abnormalities thus depends on the frequency with which blebs rest on eyes, forefeet or hind limbs, and the five types of foot abnormality depend on the exact position and size of the blebs. Blood plasma could be seen to enter these blebs in the living embryo. Green (1938) summarized all the genetical work on morphological mutations in rodents.

Absence of patellae or their delayed development is inherited, either alone or in connection with other anomalies. Little (1897) cited a family with eighteen cases in four generations, of no patella and no thumb nail. This condition was more frequent in females and was associated with hyperextension of the knee-joint. Three cases were described and forty-two found in the literature. In nine cases the knee-cap appeared at ages between six months and six years and in four it was absent at the end of the growth period. Some individuals with no patella could run and dance without difficulty. Oesterreicher's (1929) family lacked thumb nails and patella. His (1931) family showed defective patella, defective thumb nails and radius luxation. All three items of the syndrome were present in every case except two which were doubtful, one in which the luxation was unilateral and one in which only the nails were defective. These three conditions are present in 30 cases (9 ♂ 21 ♀) in four generations of another family (Senturia and Senturia, 1944), strictly dominant. A single pleiotropic gene may be concerned, or perhaps two closely linked genes, one producing the ectodermal, the other the mesodermal defects. An excess of affected females also occurred in an early family of Sedgwick with eighteen cases in four generations. Turner's (1933) two large pedigrees show small or absent patella with shoulders, elbows and ilium affected and nail dystrophy. Lester's (1936) family shows dominant inheritance of six defects in three generations: patella absent or vestigial; elbow (lower end of humerus and upper end of radius) malformed so the arm cannot be fully extended; at shoulder, head of humerus underdeveloped and scapula thickened on lateral border; ilium and in some the head of the femur abnormal; nails very thin and the nails of digits I to III have no free end; a pale peripheral zone in the iris (this may not be part of the syndrome). The cases are collected in Table 14.

In another family, Moore (1930) described *recurrent dislocation of the patella* in four generations.

TABLE 14

ABSENCE OF PATELLA

			Affected	*Normal*	■	●	□	○
Turner	1933	I	24	13	5	19	8	5
		II	26	12	13	14	7	5
Lester	1936		7	5	2	4	—	—
Oesterreicher	1931		10	10	7	4	3	7
Senturia	1944		30	14	9	21	8	6
			97	54	36	62	26	23

The condition is dominant in all families.

Absence of thumb nails (anonychia pollicum) can be inherited by itself. The nail bed is red, cartilaginous and sensitive in some cases. Ebstein (1919) described this condition in a father and two of his four children. In Menge's case a dominant pedigree included eleven affected in four generations. Cutore (1927) described an Italian family in Catania with 11 cases (5 ♂ 6 ♀) in three generations. The fingers and toes had no trace of a nail or mere vestiges in a few. This dominant pedigree showed two skips. The pedigree included a cousin marriage, DR × RR, from which there were three affected children. Strandskov (1939) found four cases of absent thumb nails, dominant in three generations of a family. The other nails were slightly abnormal — thin, slow-growing, with large and pointed lunula. Anonychia appears to be recessive in several other families, but the condition of the nails is the same.

Onychatrophy or hypoplasia of the nails overlaps anonychia. In several families the two are combined with rudimentary or absent patellae Pires de Lima (1924) described a family with onychatrophy, the nails on hands and feet more or less atrophied and deformed. A normal woman had three normal sons and twin daughters with the defect. One of these daughters had a normal son and three daughters with nails more or less atrophied. The condition was confined to the female line for two generations, but this may have been chance.

The three conditions, namely (1) anonychia or the milder form (probably an allele) absence of thumb nails only, (2) absence or defect of patella, (3) luxation of head of the radius, can thus all be inherited separately as simple dominants. From the fact that they frequently occur together as a syndrome it is probable that they are closely linked genes in one chromosome, as Aschner (1934) points out. She collected eight pedigrees of hypoplasia of the patella. In three of them the bone defect is associated constantly with a defect of the thumb nails. In a few other pedigrees other nails are also affected and other bones deformed. Nail defect also appears to be linked with alopecia. She assumes that the genes for nail and patella defect are so closely linked that they frequently mutate together. The radius defect occurs alone in a number of pedigrees and is probably not quite so closely linked as the other two. Trauner and Rieger (1925) found camptodactyly associated in a family (six cases) with the Turner triple syndrome, so it is probably more loosely linked in the same chromosome. An explanation of this syndrome based on modifiers of one gene with polyphenic aspects has been suggested, but seems less likely. On the other hand, when alopecia is associated with nail defects, both appear to be effects of one gene, but hypothyroidism appears to be a separate gene in the same linkage group.

It is generally assumed that serious defects in wild animals are "removed" by natural selection. That this is not always so is shown by Schultz' (1944) study of anatomical variation in the gibbons. Among nearly three hundred specimens and skeletons from northern Siam, where they occur in thousands, he found that 16 per cent of the skeletons of *Hylobates lar* had marked congenital digital defects, 26 per cent had congenital malformations of the teeth and nearly half of these animals, shot wild, had one or more skeletal or tooth abnormalities, similar to those in man but with a much higher frequency. Cases of fused radius and ulna occurred. Dental caries was absent in juveniles but present in 1 per cent of adults and 9 per cent of old animals. There were 115 healed fractures, especially in the humerus and femur, but some even in the skull. These observations clearly contradict the assumption of the prevalence of normality and health in wild primates. They show that in some circumstances natural selection fails to act.

LITERATURE

Abbott, F. C. 1892. Hereditary congenital dislocations of the radius. *Trans. Pathol. Soc. Lond.* 43:129–139. Figs. 3.

Adams, F. H. & Oliver, C. P. 1945. Hereditary deformities in man due to arrested development. *J. Hered.* 36:2–7. Figs. 5.

Allan, W. 1939. Inheritance of short finger tendons. *J. Hered.* 30:218.

Anton, J. I., Reitz, G. B. & Spiegel, M. B. 1938. Madelung's deformity. *Ann. Surgery* 108:411–439. Figs. 8.

Aschner, B. 1929. Zur Erbbiologie des Skelettsystems. *Zeits. f. Konst-Lehre* 14:129–211. Figs. 35.

———. 1934. A typical hereditary syndrome. *J. Am. Med. Assn.* 102: 2017–2020. Fig. 1.

Ask-Upmark, E. 1936. On sireniform malformations. *Anat. Anz.* 82:241–259. Figs. 5.

Atwood, E. S. & Pond, C. P. 1917. A polydactylous family. *J. Hered.* 8:96.

Badgley, C. E. 1943. Correlation of clinical and anatomical facts leading to a conception of the etiology of congenital hip dysplasias. *J. Bone & Joint Surg.* 25:503–523.

Bagg, H. J. 1929. A morphological study with special reference to the etiology of club-feet, syndactylism, hypodactylism, and congenital amputation in the descendants of X-rayed mice. *Am. J. Anat.* 43:167–219. Pls. 5.

Bailey, S. d'A. 1938. A pedigree of syndactylism. *J. Hered.* 29:467–468. Figs. 2.

Ballowitz, E. 1904. Über hyperdaktyle Familien und die Vererbung der Vielfingerigkeit des Menschen. *Arch. f. Rass. u. Ges.-Biol.* 1:347–365. Figs. 11.

Basler, A. 1926. Über die Häufigkeit der Zygodaktylie bei der Tübinger Bevölkerung. *Zeits. f. Morph. u. Anthrop.* 26:59–67.

Bates, Daisy. 1939. *The Passing of the Aborigines.* New York. Pp. 258.

Baumann, L. & Landauer, W. 1943. Polydactyly and anterior horn cells in fowl. *J. Compar. Neurol.* 79:153–163. Fig. 1.

Bean, A. M. 1929. A morphological analysis of the foot abnormalities occurring in the descendants of X-rayed mice. *Am. J. Anat.* 43:221–246. Figs. 14.

Becker, P. E. 1939. Unterschiedliche phänotypische Ausprägung der Anlage zur Brachymesophalangie in einer Sippe. *Zeits. f. Konst-lehre* 23:235–248. Figs. 7.

Bell, Julia. 1930. Some new pedigrees of hereditary disease. A. polydactylism and syndactylism. *Ann. of Eugen.* 4:41–48. Pls. 10.

———. 1931. Three further cases of hereditary digital anomaly seen in the out-patient Department of Great Ormond Street Hospital for Sick Children. *Ann. of Eugen.* 4:233–237. Pls. 8.

Bingham, R. 1944. Painful feet. *J. Am. Med. Assn.* 124:283–286. Figs. 7.

Boinet. 1898. Polydactylie et atavisme. *Rev. de Méd.* 18:316–328. (Cited from Bell.)

Bonnevie, K. 1919. Polydaktyi i norske bygdeslegter. *Norsk Mag. f. Lägev.* No. 6. Pp. 32.

Bonnevie, K. 1934. Embryological analysis of gene manifestation in Little and Bagg's abnormal mouse tribe. *J. Exp. Zool.* 67:443–520. Figs. 27.

———. 1936. Vererbbare Gehirnanomalie bei kurzeschwänzigen Tanzmäusen. *Acta Path. et Microbiol. Scand. Suppl.* 26. Pp. 20–27.

Boorstein, S. W. 1926. Symmetrical congenital brachydactylia. *Surg. Gynec. & Obstet.* 43:654–658. Figs. 10.

Brailsford, J. F. 1945. Familial brachydactyly. *Brit. J. Radiol.* 18:167–172. Figs. 21.

Brandeis, J. W. 1915. Polydactylism as a hereditary character. *J. Am. Med. Assn.* 64:1640–1642. Figs. 6.

Breitenbecher, J. K. 1923. Hereditary shortness of thumbs. *J. Hered.* 14:15–22. Figs. 11.

Brody, L. J. 1934. Polydactylism in five generations. *Am. J. Dis. Child.* 47:701–702.

Brown, E. 1943. An isolated human case of malformed upper extremities and thorax. *J. Hered.* 34:284–288. Figs. 5.

Browne, D. 1936. Congenital deformities of mechanical origin. *Proc. Roy. Soc. Med.* 29:1409–1431. Figs. 29.

Bryn, H. 1926. (Brief review of the anthropology of the Norwegian people.) *Norsk Tidsskr. f. Mil.-Med.* 29:1–46.

Buettner, G. 1938. Ulnare Polydaktylie bei Ulnaverdoppelung und Radiusdefekt. *Zeits. f. Konst-lehre* 22:428–440. Figs. 6.

Cady, L. D. & Francis, B. F. 1927. The supracondyloid process in the feeble-minded. *Am. J. Phys. Anthrop.* 10:387–391.

Callan, R. 1942. Polydactyly in a negro family. *J. Hered.* 33:229–232. Figs. 3.

Carlisle, Anthony. 1814. An account of a family having hands and feet with supernumerary fingers and toes. *Phil. Trans. Roy. Soc.* 104:94–101.

Castle, W. E. 1923. Further data on webbed toes. *J. Hered.* 14:209–210.

Chilton, N. 1927. Hereditary deformity of the fingers. *Brit. Med. J.* ii. 15.

Clark, W. E. LeGros. 1916. A case of hereditary syndactyly. *Lancet* ii. 434. Fig. 1.

Cohn, B. N. E. & Ravin, A. 1941. An unusual case of brachydactyly. *J. Hered.* 32:45–48. Figs. 4.

Cole, A. E. 1935. Inheritance of a fused joint in the index finger. *J. Hered.* 26:224–228. Figs. 3.

Cook, R. 1935. Too few fingers — and too many. *J. Hered.* 26:457–462. Figs. 5.

Cragg, E. & Drinkwater, H. 1916. Hereditary absence of phalanges through five generations. *J. Genet.* 6:81–89. Pl. 1.

Cummins, H. 1932. Spontaneous amputation of human supernumerary digits: pedunculated postminini. *Am. J. Anat.* 50:381–416. Pls. 2.

Cushing, Harvey. 1916. Hereditary ankylosis of the proximal phalangeal joints (symphalangism). *Genetics* 1:90–106. Figs. 11.

Cutore, G. 1927. Sterethonichia (mancanza di unghie) ereditaria. *Rivista di Biol.* 9:1–10.

Cutter, R. T. & Nelson, W. M. 1931. A short-toed family. *J. Hered.* 22:163–166. Figs. 4.

Danforth, C. H. 1919a. The developmental relations of brachydactyly in the domestic fowl. *Am. J. Anat.* 25:97–115. Figs. 5.

———. 1919b. Evidence that germ cells are subject to selection on the basis of their genetic potentialities. *J. Exp. Zool.* 28:385–412.

Daniel, G. H. 1936. A case of hereditary anarthrosis of the index finger, with associated abnormalities in the proportions of the fingers. *Ann. of Eugen.* 7:281–297. Pls. 3.

Dankmeijer, J. 1935. Congenital absence of the tibia. *Anat. Record* 62:179–194. Figs. 4.

Davenport, C. B. 1933. An alleged case of inheritance of acquired characters. *Amer. Nat.* 67:549–558. Figs. 6.

Davenport, C. B., Taylor, H. L. & Nelson, L. A. 1924. Radio-ulnar synostosis. *Arch. Surgery* 8:705–762. Figs. 49.

Davies, D. J. 1930. Congenital radio-ulnar synostosis. *Brit. Med. J.* ii. 557–558. Figs. 5.

Debrunner, H. 1940. Zur Frage der Vererbung des angeborenen Klumpfusses. *Arch. J. Klaus-Stift.* 15:185–193.

Dehus, D. & Snyder, L. H. 1932. Dominance in man, with especial reference to polydactylism. *Ohio J. Sci.* 32:232–236.

Drey, J. 1912. Hereditäre Brachydactylie kombiniert mit Ankylose einzelner Fingergelenke. *Zeits. f. Kinderhlk.* 4:553–561.

Drinkwater, H. 1908. An account of a brachydactylous family. *Proc. Roy. Soc. Edinb.* 28:35–57. Figs. 11.

———. 1912. Account of a family showing minor brachydactyly. *Compt. Rend. 4e Conf. Internat. de Genetique, Paris* Pp. 549–562. Figs. 14.

———. 1914. Minor-brachydactyly, No. 2. *J. Genet.* 3:217–220. Pls. 3.

———. 1915. A second brachydactylous family. *J. Genet.* 4:323–340. Pls. 5, figs. 3.

———. 1916. Hereditary abnormal segmentation of the index and middle fingers. *J. Anat. & Physiol.* 50:177–186. Figs. 14.

———. 1917. Phalangeal anarthrosis (synostosis, ankylosis) transmitted through fourteen generations. *Proc. Roy. Soc. Med.* 10 (Sect. Pathology): 60–68. Figs. 4.

Drysdale, J. H. & Herringham, W. P. 1908. An undescribed form of dwarfism associated with a spatulate condition of the hand. *Quart. Med. J.* 1:193–197. Pls. 4.

Duckworth, D. 1889. *A Treatise on Gout.* London. (P. 71.)

Duncan, F. N. 1917. Orthodactyly. *J. Hered.* 8:174–175. Figs. 2.

Ebstein, E. 1919. Angeborene familiäre Erkrankungen an den Nageln. *Derm. Wochens.* 68:113–124. Figs. 5.

Ebstein, E., in Heller, *Die Krankheiten der Nägel.* 1927.

Ellsworth, H. A. 1927. Inheritance of carpal displacement. *J. Hered.* 18:132–133. Figs. 2.

Faber, A. 1938. Untersuchungen ueber die Aetiologie und Pathogenese der angeborenen Hüftverrenkung; eine roentgenologisch-erbklinische Studie. *Leipzig.* Pp. 77, pls. 45.

Fantham, H. B. 1924. Heredity in man: its importance both biologically and educationally. *S. African J. Sci.* 21:498–527. Figs. 15.

Farabee, W. C. 1905. Inheritance of digital malformations in man. *Papers, Peabody Mus., Harvard Univ.* 3:65–78.

Fell, Honor B. 1934. Experiments on the development *in vitro* of the avian knee-joint. *Proc. Roy. Soc.* 116 B:316–351. Pls. 4, figs. 39.

———. 1940. The application of tissue culture *in vitro* to embryology. *J. Roy. Micr. Soc.* 60:95–112. Pl. 1, Figs. 2.

Fell, Honor B. & Robison, R. 1929. The growth, development and phosphatase activity of embryonic avian femora and limb-buds cultivated *in vitro.* *Biochem. J.* 23:767–784. Pls. 3.

Fetscher, R. 1922a. Ein Stammbaum mit Spalthand. *Arch. f. Rass. u. Ges.-Biol.* 14:176–177.

———. 1922b. Über die Erblichkeit des angeborenen Klumpfusses. *Arch. f. Rass. Biol.* 14:39–52, 140–158.

Fischer, F. J. & Vandemark, R. E. 1945. Bilateral symmetrical brachymetacarpalia and brachymetatarsalia. *J. Bone & Joint Surg.* 27:145–148. Figs. 5.

Fortuyn, A. B. D. 1939. A polydactylous strain of mice. *Genetica* 21:97–108.

Frädrich, G. 1936. Beitrag zur Frage der Sirenenbildung. *Virchow's Arch.* 297:485–494. Figs. 10.

Frere, J. M. 1930. A case having thumbs with three phalanges simulating fingers. *So. Med. J.* 23:536–537. Figs. 2.

Freud, P. & Slobody, L. B. 1943. Symphalangism. *Am. J. Dis. Child.* 65:550–557. Figs. 5.

Gates, R. R. 1933. A form of brachyphalangy in a cousin marriage. *Lancet* 224:194.

Gillette, C. P. 1931. An inheritable defect of the human hand. *J. Hered.* 22:189–190. Figs. 2.

Gilmore, E. R. W. 1927. Hereditary deformity of the fingers. *Brit. Med. J.* ii. 935–936.

Glass, L. C. & Magee, E. 1935. The inheritance of crooked little fingers. *J. Hered.* 26:490.

Glasstone, S. 1938. A comparative study of the development *in vitro* and *in vivo* of rat and rabbit molars. *Proc. Roy. Soc.* 126 B:315–330. Pls. 3, figs. 9.

Gluecksohn-Schoenheimer, G. & Dunn, L. C. 1945. Sirens, aproposi and intestinal abnormalities in the house mouse. *Anat. Rec.* 92:201–213. Figs. 3.

Goldflam, S. 1906. Ein Fall von kongenitaler familiärer Ankylose der Fingergelenke. *Münch. Med. Wochens.* 53:2299–2300. Fig. 1.

Grebe, H. 1940. Untersuchungen über Papillarlinienveränderungen bei Syndaktylie und Polydaktylie. *Zeits. f. Morph. u. Anthr.* 39:62–78. Pls. 7.

Green, C. V. 1938. Homologous and analogous morphological mutations in rodents. *Biol. Reviews* 13:293–306.

Greene, H. S. N. & Saxton, J. A., Jr. 1939. Hereditary brachydactylia and allied abnormalities in the rabbit. *J. Exp. Med.* 69:301–314. Pls. 3.

Gruber, W. 1870. Zusammenstellung veröffentlichter Fälle von Polydactylie mit 6 Fingern an der Hand und 6 Zehen an dem Fusse; und Beschreibung zweier neuen Fälle von Duplicität das Daumens. *Bull. Acad. Imp. St. Petersburg* 15:459–483. Pl. 1, fig. 1.

Günther, R. 1939. Zur Frage der angeborenen Amputationen. *Zeits. f. Konst-lehre* 23:736–758. Figs. 37.

Gutmann, M. J. 1925. Zur Vererbung der Hammerzehe. *Arch. f. Rass. Biol.* 17:190.

Hall, G. A. M. 1928. Hereditary brachydactylism and interphalangeal ankylosis. *Ann. of Eugen.* 3:265–268. Pls. 4.

*Hart, V. L. 1942. Primary genetic dysplasia of the hip with and without classical dislocation. *J. Bone & Joint Surg.* 24:753–771.

Hawkes, O. A. M. 1914. On the relative lengths of the first and second toes of the human foot, from the point of view of occurrence, anatomy and heredity. *J. Genet.* 3:249–274. Pls. 3, figs. 6.

Heberden, W. 1803. *Commentaries on the History and Cure of Diseases.* 2nd edn. London. Pp. 518.

Hegdekatti, R. M. 1939. Congenital malformation of hands and feet in man. *J. Hered.* 30:191–196. Figs. 5.

Hefner, R. A. 1924a. Symphalangism. *J. Hered.* 15:323–329. Figs. 6.

———. 1924b. Subterminal articulation in the proximal joint of the little finger. *J. Hered.* 15:481–483. Figs. 3.

———. 1924c. Short thumbs (brachymegalodactylism). *J. Hered.* 15:432–439. Figs. 9.

———. 1929. Inheritance of crooked little fingers (streblomicrodactyly). *J. Hered.* 20:395–398. Figs. 4.

———. 1941. Crooked little fingers. *J. Hered.* 32:37–38. Figs. 2.

Henry, M. G. 1945. Anomalous fusion of the scaphoid bone and the greater multangular bone. *Arch. of Surgery* 50:240–241. Figs. 3.

Herzog, A. 1927. Missbildung im Ellenbogengelenk. Eine unbekannte Anomalie. *Fortschr. Geb. d. Röntgenstr.* 36:407–409. Figs. 2.

Heston, W. E. 1932. Inheritance of "webbed toes." *J. Hered.* 23:378–381. Figs. 3.

Hoffman, H. 1924. Über hereditäre Kolmendaumen. *Klin. Wochens.* 3:324. Fig. 1.

———. 1928. Zur Brachyphalangie des Daumens. *Klin. Wochens.* 7:2155–2157.

Hooff, G. 1928. Ueber die Erblichkeit der angeborenen Hüftverrenkung. *Arch. f. Rass. u. Ges.-Biol.* 20:369–389.

Horsfall, F. L., Jr. 1936. Congenital clubbing of the fingers and toes. *Canad. Med. Assn. J.* 34:145–149. Figs. 6.

Hrdlička, A. 1923. Incidence of the supracondyloid process in whites and other races. *Am. J. Phys. Anthrop.* 6:405–412.

Hurlin, R. G. 1920. A case of inherited syndactyly in man. *J. Hered.* 11:334–335. Figs. 2.

Hutt, F. B. & Mueller, C. D. 1943. The linkage of polydactyly with multiple spurs and duplex comb in the fowl. *Am. Nat.* 77:70–78.

Iltis, H. 1944. A new case of typical brachydactyly. *J. Hered.* 35:145–148. Figs. 2.

Inman, O. L. 1924. Four generations of symphalangism. *J. Hered.* 15:329–334. Figs. 5.

Jackson, V. W. 1937. Four generations of polydactyly. *J. Hered.* 28:267–268.

Johansson, I. 1942. Two mutant characters in Swedish cattle. *Hereditas* 28:278–288. Figs. 5.

Johnson, L. E. 1940. "Streamlined" pigs. *J. Hered.* 31:239–242. Figs. 2.

Kammeier, O. F. 1927. On sireniform monsters, with a consideration of the causation and the predominance of the male sex among them. *Anat. Rec.* 34:365–389. Figs. 4.

Kayne, G. G. 1933. Familial clubbing of the fingers and toes. *Proc. Roy. Soc. Med.* 26:270–271.

Kellie, Dr. 1808. *Edinb. Med. J.* 4:252–253.

Kemp, R. & Ravn, J. 1932. Über erbliche Hand- und Fussdeformitäten in einem 140-köpfigen Geschlecht, nebst einigen Bemerkungen über Poly- und Syndaktylie beim Menschen. *Acta Psychiat. et Neurol.* 7:275–296. Figs. 29.

Key, J. A. 1927. Hypermobility of joints as a sex-linked hereditary characteristic. *J. Am. Med. Assn.* 88:1710–1713. Figs. 5.

Klein, I. J. 1932. Hereditary ectrodactylism in siblings. *Am. J. Dis. Child.* 43:136–142. Figs. 7.

Koehler, O. 1929. Zur Frage der Vererbung der Menschlichen Vielfingerigkeit. *Biol. Zentlbl.* 49:705–717; 50:119–120. 1930.

Koehler, O. 1936. Die hand- und fusslosen brasilianischen Geschwister. *Zeits. f. Vererb. u. Konst-lehre* 19:670–690. Figs. 8.

Koenner, D. M. 1934. Abnormalities of hands and feet. *J. Hered.* 25:329–334. Figs. 4.

Kuhns, J. G. 1942. Congenital flatfoot. *J. Am. Med. Assn.* 120:329–333. Figs. 7.

Lester, A. M. 1936. A familial dyschondroplasia associated with anonychia and other deformities. *Lancet* 231:1519–1521. Figs. 2.

Lewis, T. 1909a. Hereditary malformations of the hands and feet. *Treas. Hum. Inher.* pt. 1, 6–10. Pls. 3.

———. 1909b. Brachydactylism. *Treas. Hum. Inher.* pt. 1:14–17. Pls. 3.

———. 1909c. Polydactylism. *Treas. Hum. Inher.* pt. 1:10–14. Pls. 2.

Lewis, T. & Embleton, D. 1908. Split-hand and split-foot deformities, their types, origin and transmission. *Biometrika* 6:26–58. Pls. 7.

Liebenam, L. 1938a. Beitrag zum familiären Auftreten der Brachydaktylie. *Zeits. f. Konst-lehre.* 22:418–427. Figs. 15.

———. 1938b. Beitrag zum familiären Vorkommen von Spalthänden und Spaltfüssen. *Zeits. f. Konst-lehre* 22:136–151. Figs. 10.

———. 1938c. Über gleichzeitiges Vorkommen von Gliedmassenenddefekten und osteosklerotischer Systemerkrankung. *Zeits. f. Konst-lehre* 21:697–703. Figs. 6.

de Lima, J. A. Pires. 1924. Hereditary atrophy of the nails. *Ann. de Derm. et Syph.* 5:266–271. Figs. 4.

de Linares, L. G. 1930. Collective polydactylism in a small town. *J. Am. Med. Assn.* 94:2080.

Lipscomb, T. W. 1915. A study in heredity. *Med. J. Australia* 1:260–261. Figs. 5.

Little, E. M. 1897. Congenital absence or delayed development of the patella. *Lancet* ii. 781–784. Figs. 3.

Lucas, Clement. 1880. On a remarkable instance of hereditary tendency to the production of supernumerary digits. *Guy's Hosp. Reports* 3rd ser., 25:417–419.

de Lucchi, G. 1938. Considerazione sulle modalità di trasmissione ereditaria in un caso di piede torto congenito. *Chir. d. org. di Movimento* 23:287–290, 23:481–491.

Lücker, F. C. 1924. Über Vererbung von Missbildungen, insbesondere Hasenscharte und Polydaktylie, und ihre Beziehungen zur Geburtshilfe. *Monatschr. f. Geburtsh. u. Gynäk.* 66:327–336.

MacArthur, J. W. & McCullough, E. 1932. Apical dystrophy, an inherited defect of hands and feet. *Human Biol.* 4:179–207. Figs. 9.

McClintic, B. S. 1935. Five generations of polydactylism. *J. Hered.* 26:141–144. Figs. 3.

McFarland, B. 1930. *Brit. Med. J.* ii. 664.

MacKinder, D. 1857. Deficiency of fingers transmitted through six generations. *Brit. Med. J.* 1857:845–846.

McMullen, G. & Pearson, K. 1913. On the inheritance of the deformity known as split-foot or lobster claw. *Biometrika* 9:381–390. Pls. 6.

Mahaffy, H. W. 1945. Bilateral congenital calcaneocuboid synostosis. *J. Bone & Joint Surg.* 27:164–165. Figs. 2.

Manoiloff, E. O. 1931. A rare case of hereditary hexadactylism. *Am. J. Phys. Anthrop.* 15:503–508. Figs. 2.

Manson, J. S. 1915. Hereditary syndactylism and polydactylism. *J. Genet.* 5:51–63. Pls. 6.

Marshall, R. 1929. Note on a family with brachydactyly. *Arch. of Dis. in Child.* 4:385–388. Figs. 10.

Martmer, E. E. 1927. Talipomanus: a report of three cases in one family. *Am. J. Dis. Child.* 34:384–387. Pls. 2.

Ménaché, M. 1931. Polydactylie héréditaire. *Bul. Soc. d'Obstet. et Gynec. de Paris* 20:393–394.

Milles, B. L. 1928. The inheritance of human skeletal anomalies. *J. Hered.* 19:28–46. Figs. 13.

Miskolczy, D. 1929. Erbliche Verkürzung der Mittelhandknochen und Schizophrenie. *Arch. f. Psychiat.* 87:242–265. Figs. 3.

Mohr, O. L. 1921. A case of hereditary brachyphalangy utilised as evidence in forensic medicine. *Hereditas* 2:290–298. Figs. 10.

Mohr, O. & Wriedt, Chr. 1919. A new type of hereditary brachyphalangy in man. *Carnegie Inst. Wash. Publ.* No. 295, pp. 64. Pls. 7.

Moore, B. H. 1930. A case of hereditary recurrent dislocation of the patella. *J. Bone & Joint Surg.* 12:654–655.

Moore, W. G. & Messina, P. 1936. Camptodactylism and its variable expression. *J. Hered.* 27:27–30. Figs. 2.

Morand. 1773. Recherches sur quelques conformations monstrueuses des doigts dans l'homme. *Hist. de l'Acad. Roy. des Sci.* 1770:137–150. (Cited from Bell.)

Müller, W. M. 1926. Zur Aetiologie des angeborenen Klumpfusses unter besonderer Berücksichtigung seiner Vererbung. *Arch. d. Julius Klaus-Stiftung* 2:1–37.

*Müller, W. 1937. *Die angeborenen Fehlbildungen der menschlichen Hand.* Pp. 170, figs. 116. Leipzig.

Murphy, D. P. 1925. Five successive generations of webbed finger deformity. *J. Am. Med. Assn.* 84:576–577.

———. 1926. Familial finger contracture and associated familial knee-joint subluxation. *J. Am. Med. Assn.* 86:395–397. Figs. 3.

Murray, P. D. F. 1926. An experimental study of the development of the limbs of the chick. *Proc. Linn. Soc. N. S. W.* 51:187–263. Figs. 53.

Neurath, R. 1932. Ueber hereditäre "Kolbendaumen" (Brachyphalangie). *Wien Klin. Wochens.* 45:1210–1211. Figs. 3.

Newsholme, H. P. 1910. A pedigree showing bi-parental inheritance of webbed toes. *Lancet* ii. 1690–1691.

Nievergelt, K. 1944a. Positiver Vaterschaftsnachweis auf Grund erblicher Missbildungen der Extremitäten. *Arch. J. Klaus-Stift.* 19:157–195. Figs. 39.

———. 1944b. Ungewöhnliches familiäres Missbildungssyndrom beider Hände. *Ibid.* 19:197–212. Figs. 12.

Nissen, K. I. 1933. A study in inherited brachydactyly. *Ann. of Eugen.* 5:281–301. Pl. 1, figs. 31.

Nowak, H. 1934. Drei Stammbäume von Klinodaktylie. *Deuts. Med. Wochens.* 60:2001.

Nylander, E. S. 1931. Präaxiale Polydaktylie in fünf Generationen einer schwedischen Sippe. *Upsala Läkaref Förh.* 36:275–292.

Odiorne, J. M. 1943. Polydactylism in related New England families. *J. Hered.* 34:45–55.

Oesterreicher, K. 1929. Nägel und Skelettanomalien. *Wien Klin. Wochens.* 42:632.

———. 1931. Gemeinsame Vererbung von Anonychie bzw. Onychatrophie, Patellar defekt und Luxatio radii. *Zeits. f. Konst-lehre* 15:465–476. Figs. 12.

Oliver, C. P. 1940. Recessive polydactylism associated with mental deficiency. *J. Hered.* 31:365–367.

Ollerenshaw, R. 1925. Congenital defects of the long bones of the lower limb. *J. Bone & Joint Surg.* 7:528–552. Figs. 34.

Orel, H. 1928. Kleine Beiträge zur Vererbungswissenschaft. *Zeits. f. Konst-lehre* 13:691–698.

Parkes-Weber, F. 1919. The occurrence of clubbed fingers in healthy persons as a familial peculiarity. *Brit. Med. J.* ii. 379.

Parks, H. & Staples, O. S. 1945. Two cases of Morvan's syndrome of uncertain origin. *Arch. Int. Med.* 75:75–81. Figs. 5.

Peacock, W. 1929. Hereditary absence of hands and feet. *Eugen. News* 14:46–47. Fig. 1. 15:59–60, 86–87, 143–145.

Pearson, K. 1908. On inheritance of the deformity known as split-foot or lobster claw. *Biometrika* 6:69–79. Pls. 9.

———. 1931. On the existence of the digital deformity — so-called "lobster-claw" — in the apes. *Ann. of Eugen.* 4:339–340. Pls. 10.

Pendergast, W. 1936. Inheritance of short, stubby hands. *J. Hered.* 27:448. Figs. 2.

Penhallow, D. P. 1928. An unusual case of polydactylism. *J. Am. Med. Assn.* 91:564–565. Figs. 6.

Pfeiffer, R. 1937. Die Variabilität der angeborenen Femurhypoplasie (sog. kongenitaler Oberschenkeldefekt). *Zeits. f. Konst-lehre* 20:493–525. Figs. 22.

———. 1938. Die angeborene Verrenkung des Speichenköpfchens als Teilerscheinung anderer kongenitaler Ellenbogengelenkmissbildungen. *Zeits. f. Konst-lehre* 21:530–544. Figs. 11.

Pfitzner, W. 1890. Die kleine Zehe. *Arch. f. Anat. u. Physiol.* 12–41.

———. 1898. Beiträge zur Kenntnis der Missbildungen des menschlichen Extremitätenskelets. *Morph. Arbeiten* 8:304–340. Pls. 3.

Plummer, S. 1937. Family with webbed feet. *Eugen. News* 22:109–110.

Pol, Dr. 1921. "Brachydactylie," "Klinodaktylie," Hyperphalangie und ihre Grundlagen. *Virchow's Arch. f. Path. Anat.* 229:388–530. Figs. 21.

Polonskaja, R. 1936. Anatomische Eigenschaften der Menschen mit Polydaktylie. *Fol. Morph.* 7:114–120. Figs. 3.

Popenoe, Paul. 1937. Split-hand. *J. Hered.* 28:174–176. Fig. 1.

Pryor, J. W. 1907. Hereditary nature of variation in ossification of bones. *Anat. Record* 4:84–88.

———. 1936. Ossification as additional evidence in differentiating identicals and fraternals in multiple births. *Am. J. Anat.* 59:409–423. Figs. 15.

———. 1939. Normal variations in the ossification of bones. *J. Hered.* 30:249–255. Figs. 4.

Rabaud, E., 1919. Recherches sur l'hérédite et la variation. *Supp. Bull. Biol. de France et Belg.* Pp. 313.

Regnault, F. 1911. Modifications squelettiques et musculaires du chien ectromèle. *Bull. et Mem. Soc. Anthrop. Paris* 2:586–590. Figs. 2.

Rieder, H. 1889. Ueber gleichzeitiges Vorkommen von Brachy- und Hyper-phalangie an der Hand. *Deut. Arch. Klin. Med.* 66:330–348. Figs. 6.

———. 1900. Eine Familie mit dreigliedrigen Daumen. *Zeits. f. Morph. u. Anthrop.* 2:177–197. Figs. 13.

Ritterskamp, P. 1936. Eine Familie mit Kamptodaktylie. *Münch. Med. Wochens.* 83:724–725. Figs. 3.

Roberts, E. 1943. Hereditary hyperphalangism of the thumb. *J. Hered.* 34:291–292. Fig. 1.

Roch, G. 1925. Die Vererbung der sogenannten angeborenen Hüftverrenkung. *Arch. f. Rass. u. Ges.-Biol.* 17:241–255.

Rochlin, D. G. 1928. Über die hereditäre symmetrische Gelenkhypoplasie. *Zeits. f. Konst-lehre* 13:654–663. Figs. 4.

Roth, P. B. 1926. Congenital synostosis of humerus and radius occurring in three children of one family. *Proc. Roy. Soc. Med.* 19:51–52. Figs. 2.

Roth, W. E. 1911–1912. Animism and folk-lore of Guiana Indians. *Bur. of Amer. Ethnol.*, Rept. No. 153, p. 364.

Rudert, Ilse. 1938. Über die Vererblichkeit der präaxialen Polydaktylie. *Zeits. f. Konst-lehre* 21:545–557. Figs. 5.

Sayles, L. P. & Jailer, J. W. 1934. Four generations of short thumbs. *J. Hered.* 25:377–378. Figs. 2.

Schade, H. 1937. Zur endogenen Entstehung von Gliedmassendefekten. *Zeits. f. Morph. u. Anthrop.* 36:375–381. Pls. 4.

Scherb, R. 1939. Zur Frage der verschiedenen Erbfaktoren beim angeborenen Klumpfuss. *Schweiz. Med. Wochens.* 69:998–1001. Figs. 8.

Schinz, H. R. 1943. Erbtypen und Formen bei Brachydaktylie. *Arch. J. Klaus-Stift.* 18:361–404. Figs. 42.

Schlaginhaufen, O. 1934. Über familiäres Vorkommen der Überstreckbarkeit der Gelenke der Hand. *Zeits. f. Morph. u. Anthrop.* 34:386–397. Figs. 2.

Schofield, R. 1922. Inheritance of webbed toes. *J. Hered.* 12:400–401.

Schroeder, E. 1918. Entstehung und Vererbung von Missbildungen an der Hand eines Hypodaktyliestammbaumes. *Monatsschr. Geburtsh. u. Gynäkol.* 48:210–222. Pls. 3, figs. 7.

Schultz, A. H. 1922. Zygodactyly and its inheritance. *J. Hered.* 13:113–117. Figs. 4.

———. 1934. Some distinguishing characters of the mountain gorilla. *J. of Mammalogy* 15:51–61. Figs. 2.

———. 1944. Age changes and variability in gibbons. *Am. J. Phys. Anthrop.* N.S. 2:1–129. Figs. 30.

Scott, W. 1933. Syndactylism with variations. *J. Hered.* 24:241–243. Figs. 6.

Seaton, D. R. 1938. Familial clubbing of the fingers and toes. *Brit. Med. J.* i. 614–615. Fig. 1.

Senturia, H. R. & Senturia, B. D. 1944. Congenital absence of the patellae associated with arthrodysplasia of the elbows and dystrophy of the nails. *Am. J. Roentgenol.* 51:352–358. Figs. 6.

Shafar, J. 1941. Hereditary short digits. *Brit. J. Radiol.* 14:396–402. Figs. 7.

Shevkenek, W. & Thompson, W. P. 1933. A case of recessive polydactylism. *Trans. Roy. Soc. Can.*, Sect. V. 27:169–171. Fig. 1.

Siemens, H. W. 1923. Einführung in die allgemeine und spezielle Vererbungspathologie des Menschen. *Berlin: Springer.* Pp. 286, figs. 94.

Sinha, S. 1918. Polydactylism and tooth color. *J. Hered.* 9:96.

Sloane, D. 1943. Madelung's deformity in sisters. *Am. J. Surg.* 60:272–276. Figs. 6.

Smith, W. R. & Norwell, J. S. 1894. Hereditary malformation of the hands and feet. *Brit. Med. J.* ii. 8–11. Figs. 5.

Snyder, L. H. 1929. A recessive factor for polydactylism in man. *J. Hered.* 20:73–77. Figs. 4.

Sommer. 1916. Cited from Straus, 1926.

Stecher, R. M. 1940. Heberden's nodes: the incidence of hypertrophic arthritis of the fingers. *New Engl. J. Med.* 222:300–308. Figs. 2.

———. 1941. Heberden's nodes: heredity in hypertrophic arthritis of the finger joints. *Am. J. Med. Sci.* 201:801–809. Figs. 5.

Stecher, R. M. & Hersh, A. H. 1944. Heberden's nodes: the mechanism of inheritance in hypertrophic arthritis of the fingers. *J. Clin. Investig.* 23:699–704.

Steggerda, M. 1942. Inheritance of short metatarsals. *J. Hered.* 33:233–234. Figs. 3.

Stieve, H. 1916. Über Hyperphalangie des Daumens. *Anat. Anz.* 48:565–581. Fig. 1.

Stiles, K. A. 1939. The inheritance of brachymetapody. *J. Hered.* 30:87–91. Figs. 2.

Stiles, K. A. & Dougan, P. 1940. A pedigree of malformed upper extremities. *J. Hered.* 31:65–72. Fig. 7.

Stiles, K. A. & Pickard, I. S. 1943. Hereditary malformations of the hands and feet. *J. Hered.* 34:341–344. Figs. 4.

Stiles, K. A. & Schalck, J. 1945. A pedigree of curved forefingers. *J. Hered.* 36:211–216. Figs. 4.

Stiles, K. A. & Weber, R. A. 1938. A pedigree of symphalangism. *J. Hered.* 29:199–202. Figs. 3.

Stockard, C. R. 1936. An hereditary lethal for localized motor and preganglionic neurones with a resulting paralysis in the dog. *Am. J. Anat.* 59:1–53. Pls. 10, figs. 3.

———. 1941. *The Genetic and Endocrine Basis for Differences in Form and Behavior.* Philadelphia: Wistar Institute. Pp. 775.

Stoddard, S. E. 1939. Nomenclature of hereditary crooked fingers. *J. Hered.* 30:511–512. Figs. 5.

Strandskov, H. H. 1939. Inheritance of absence of thumb nails. *J. Hered.* 30:53–54. Figs. 2.

Straus, Wm. L., Jr. 1926. The nature and inheritance of webbed toes in man. *J. Morph.* 41:427–439. Figs. 19.

Strayer, L. M., Jr. 1943. The embryology of the human hip joint. *Yale J. of Biol. & Med.* 16:13–26. Figs. 18.

Streeter, G. L. 1930. Focal deficiencies in fetal tissues and their relation to intra-uterine amputation. *Carnegie Inst. Wash. Publ.* No. 126.

Ströer, W. F. H. 1935. Familiäres Auftreten von Hand- und Fussabweichungen in fünf Generationen. *Genetica* 17:299–312. Pls. 2, Figs. 5.

Struthers, J. 1873. On hereditary supra-condyloid process in man. *Lancet* i. 231–232. Figs. 2.

Sturkie, P. D. 1941. Hypermobile joints in all descendants for two generations. *J. Hered.* 32:232–234. Figs. 2.

———. 1943. Suppression of polydactyly in the domestic fowl by low temperature. *J. Exp. Zool.* 93:325–346. Figs. 3.

Sverdrup, A. 1922. Postaxial polydactylism in six generations of a Norwegian family. *Journ. Genetics* 12:217–240. Pls. 6.

Sysak, N. 1928. About hearths of polydactyly in the Poltava Government. *Zeits. f. Konst-lehre* 12:463–468.

Terry, R. J. 1930. On the racial distribution of the supracondyloid variation. *Am. J. Phys. Anthrop.* 14:459–462.

Terry, R. J. & Cady, L. D. 1923. Comparison of the incidence of the supracondyloid process in groups with normal and abnormal mentality. *Eugenics, Genetics and the Family.* Baltimore.

Thomas, A. R. 1936. A new dystrophy of the fifth finger. *Lancet* 230: 1412–1413. Figs. 3.

Thomas, L. C. 1926. Radio-ulnar olisthy. *Eugen. News* 11:150–153. Figs. 3.

Thomsen, O. 1927. Einige Eigentümlichkeiten der erblichen Poly- und Syndaktylie bei Menschen. *Acta Med. Scand.* 65:609–644. Figs. 53.

———. 1928. Hereditary growth anomaly of the thumb. *Hereditas* 10:261–273. Figs. 12.

Tomesku, I. 1928. Kongenitale Deviationen der Phalangen. Angeborene Contracturen der Finger und Klinodaktylien. *Arch. f. Orthop. u. Unfall-Chir.* 26:126–137. Figs. 7.

Töndury, G. 1944. Zur Kenntnis der Fehlbildungen mit Defekten des hinteren Körperendes. *Arch. J. Klaus-Stift.* 19:225–264. Figs. 12.

Trauner, R. & Rieger, H. 1925. Eine Familie mit 6 Fällen von Luxatio radii congenita mit übereinstimmenden Anomalien der Finger- und Kniegelenke, sowie der Nagelbildung in 4 Generationen. *Arch. f. Klin. Chir.* 137:659–666. Figs. 6.

Tubby, A. H. 1894. A case of "lobster-claw" deformity of the feet and partial suppression of the fingers, with remarkable hereditary history. *Lancet* i. 396–397. Figs. 4.

Tucker, W. E. 1934. A family with congenital absence of the heads of the femora. *Proc. Roy. Soc. Med.* 27:573–574. Figs. 4.

Turner, J. W. 1933. An hereditary arthrodysplasia associated with hereditary dystrophy of the nails. *J. Am. Med. Assn.* 100:882–884. Figs. 6.

Veit, G. 1939. Über familiäres Vorkommen von Oligodaktylie. *Zeits. f. Konst-lehre* 23:620–635. Figs. 15.

Vidal, E. 1910. Brachydactylie symmétrique, et autres anomalies osseuses, héréditaires de plusieurs générations. *Bull. de l'Acad. Med. Paris* 63:632–648. Figs. 4.

Walker, G. 1901. Remarkable cases of hereditary anchyloses, or absence of various phalangeal joints, with defects of the little and ring fingers. *Johns Hopkins Hosp. Bull.* 12:129–133. Pls. 2.

Walter, Mable R. 1938. Five generations of short digits. *J. Hered.* 29:143–144. Fig. 1.

Warkany, J. & Nelson, R. C. 1941. Skeletal abnormalities in the offspring of rats reared on deficient diets. *Anat. Rec.* 79:83–100. Figs. 10.

Warkany, J. & Schraffenberger, E. 1944. Congenital malformations induced in rats by maternal nutritional deficiency. *J. Nutrition* 27: 477–484.

Wegelin, C. 1917. Über eine erbliche Missbildung des kleinen Fingers. *Berl. Klin. Wochens.* 54. No. 12.

Weidenreich, F. 1923. Die Zygodaktylie und ihre Vererbung. *Zeits. f. Abst. u. Vererb.* 32:304–311.

White, E. H. 1944. Bilateral congenital fusion of carpal capitate and hamate. *Am. J. Roentgenol.* 52:406–407. Figs. 2.

Whitney, L. F. 1932. Inheritance of doublejointedness in the thumb. *J. Hered.* 23:425–426. Figs. 2.

Wightman, J. C. 1937. A pedigree of syndactyly. *J. Hered.* 28:421–423. Fig. 1.

Wile, I. S. 1922. Another pedigree of webbed toes. *J. Hered.* 13:118.

Willis, R. A. 1935. Experiments on the intracerebral implantation of embryo tissues in rats. *Proc. Roy. Soc.* 117B:400–412. Pls. 2.

———. 1936. The growth of embryo bones transplanted whole in the rat's brain. *Proc. Roy. Soc.* 120B:496–498. Pl. 1.

Wilmoth, C. L. 1930. Hereditary joint abnormalities: case report. *Southern Med. J.* 23:1001–1002. Figs. 3.

Witherspoon, J. T. 1936. Congenital and familial clubbing of the fingers and toes, with a possibly inherited tendency. *Arch. Int. Med.* 57:18–31. Figs. 2.

Wolff, F. 1921. Ein Fall dominanter Vererbung von Syndaktylie. *Arch. f. Rass. u. Ges.-Biol.* 13:74–75.

Wright, S. 1934. Polydactylous guinea pigs. *J. Hered.* 25:359–362. Figs. 5.

———. 1935. A mutation of the guinea pig, tending to restore the pentadactyl foot when heterozygous, producing a monstrosity when homozygous. *Genetics* 20:84–107. Figs. 5.

Yap, E. & Pineda, E. V. 1922. Two interesting cases of ectrosyndactyly. *Philippine J. Sci.* 20:1–11. Pls. 6.

Zirkle, C. 1936. Further notes on pangenesis and the inheritance of acquired characters. *Amer. Nat.* 70:529–546.

Zurukzoglu, St. 1929. Über eine erbliche Missbildung des kleinen Fingers. *Arch. d. J. Klaus-Stift.* 4:217–218.

Chapter XII

ANOMALIES OF THE SKELETON AND OF BONE STRUCTURE

SINCE the discovery of X rays, various abnormal conditions of the bony tissues have been discovered which could not previously be observed. Other abnormalities of bone structure have been seen in Neolithic skeletons and in vertebrate fossils as far back as the Cretaceous.

A condition which is frequently called *marble bones* and has also been misnamed *osteosclerosis* and *osteopetrosis* was discovered accidentally by X rays and described by Albers-Schönberg in 1904. It is rare, but about thirty cases were described in thirty years, mainly in Germany; a few in Switzerland, France, Italy and America. The cortex of the long bones becomes greatly thickened at the expense of the medulla, which may be entirely obliterated, thus doing away with the hemopoietic (blood-producing) function of the bone marrow. These bones fracture and become deformed easily. The condition is generally found in sibs (recessive), but is probably an irregular dominant in some families, as it occurred in a father and son and in a mother and three children. There were four cases in a family from Heligoland where inbreeding has been common for generations. Karshner (1926) described four cases ranging in age from one to eleven years among 2500 children X-rayed. He found twenty-six cases in the literature. The face becomes characteristically "old" in appearance, but the blood calcium was normal in the cases tested. There may be derangement of phosphorus metabolism but the mentality is generally normal.

In a French family in Montreal, the mother and three children were affected. Pirie (1930) described this family and also a single unrelated case. The bones, while impervious to X rays, are found to be soft and easily cut with a knife — more like chalk than marble. Kudrjawtzewa (1930) described the case of a boy of three and a half years, who died fifteen months later with great enlargement of liver and spleen, which compensates for the loss of bone marrow. He regarded the condition as recessive in inheritance. Pounders (1935) considered the etiology of this condition. Secondary symptoms are anaemia and hydrocephalus. Probably many cases die *in utero* and others soon after birth. A hyperparathyroid origin of the disease is suggested.

An aberrant form in two brothers was described by Field (1938). Van Creveld and Heybroek (1940) have an extended discussion of the disease. Herzenberg and Levit (1931) described two Russian families with five cases from normal parents and recognized two forms. In one heterozygous individual the condition was mildly expressed. Hanhart (1942) recognizes three forms, all recessive. In (*a*) the condition becomes malignant. He cites a Swiss family (1943) dating from an eighteenth-century marriage. The more frequent form (*b*) is lethal in childhood, following anaemia. In another group (*c*) the marrow changes to bone, producing fractures but not marked anaemia.

Spotted bones, *osteopoikily*, *osteopathia condensans* and *ostitis condensans disseminata* are names for another rare familial change in the skeleton, which was discovered by X rays. This was also described by Albers-Schönberg (1915) in a soldier in Hamburg. The bones were not brittle. Dense spots or areas of condensation are present in the spongiosa of the bones (Fig. 173). This mutational defect of the skele-

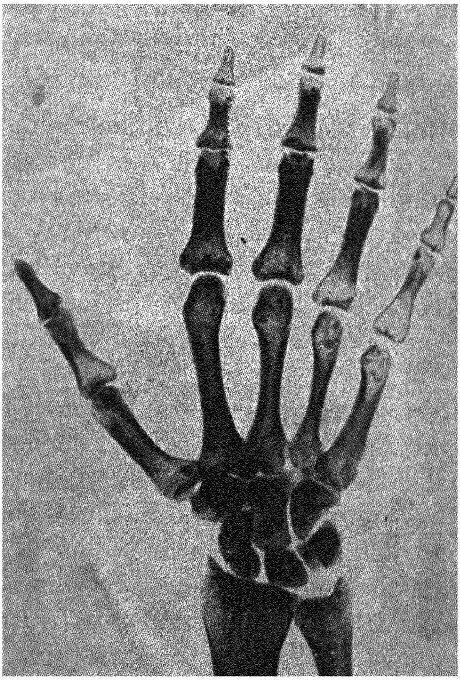

Fig. 173. Skiagraph of hand showing denser spots in bones. (After Wilcox)

ton is accompanied by a condition of the skin known as *dermatofibrosis lenticularis disseminata,* in which there are small, hard nodules loose in the skin of the seat, thigh and trunk. They are composed of connective tissue in the skin and subcutis. Windholz (1932) described a father and daughter with "spotted bones" and "spots" in the skin. The changes appear to be analogous and are probably both due to one gene. A third, unrelated case showed the same changes in the bones and skin, but the knee bones (around the joint) were longitudinally striped. Wilcox (1932) found the condition in father and son. Brücke (1933) found about twenty-six cases recorded and described one in a man and child (apparently male). It appears to be more frequent in males. All the bones are generally involved except the skull, spine and ribs, or skull, spine, scapula and clavicle. The method of inheritance is still uncertain.

A closely related condition is the conspicuous longitudinal *striping of the bones* as enostoses in the same places, i.e., calcaneum, tibia, fibula, femur, arm bones, etc. Voorhoeve (1924) described this condition in father, son and daughter.

Caffey and Silverman (1945) describe under the term *infantile cortical hyperostoses* a new condition in which the tubular limb bones, ribs, clavicles, scapulae and mandible are so affected by hyperostosis that the cavity may be partly occluded, as shown by X-rays. Four cases are described, all male infants, and three others are mentioned. It is accompanied or preceded by swelling of the face or limbs, but no evidence of infection could be found. The possibility of inheritance should be explored.

Osteogenesis imperfecta (brittle bones), *osteitis deformans* (Paget's disease) and generalized osteitis fibrosa (Recklinghausen's disease) are related conditions in which the calcium and phosphorus metabolism are involved, and possibly the parathyroids. All show defective calcification of bone and liability to fractures. The plasma phosphatase, which is responsible for the deposition of calcium from phosphoric esters in the blood, is high. In connection with osteogenesis imperfecta and osteitis deformans, otosclerosis may develop. Jaffe, Bodansky and Blair (1930) showed that bone destruction similar to osteitis fibrosa in man could be induced in guinea pigs and dogs by large doses of Collip's parathyroid hormone. Crooks (1932) published a dominant pedigree of osteogenesis imperfecta with 12 cases (3♂ 9♀) in four generations. One child was delivered by Caesarean section with a broken femur and blue sclerotics and a bitemporal bulge. In another family the mother had osteitis deformans, a daughter of seven weeks osteogenesis imperfecta and congenital pyloric stenosis, blue sclerotics and a bitemporal bulge. She broke her left radius and femur in her cot.

Roberts and Cohen (1926) state that an Egyptian mummy and even a Neanderthal skull are believed to show Paget's disease. It is also known in monkeys, horses and other animals. They found over three hundred human cases recorded, to which they added 16 (11 ♂ 5 ♀). Pain in the legs is accompanied by progressive decalcification of old bone and its replacement by an osteoid tissue. The term *osteitis deformans* was coined for it independently by Czerny in 1873 and by Paget in 1877. Roberts and Cohen found thirteen cases of familial incidence in the literature, and two of their patients were sisters. Kay, Simpson and Riddoch (1934) describe a case in brother and sister, the mother also probably affected, but the manner of inheritance is not yet clear. In another family (Weber and Huber, 1939) three sisters were affected at ages 62 to 72, their nine brothers being normal.

Twelve cases of osteitis deformans were studied by Moehlig and Murphy (1935) who concluded that constitutional inheritance plays the major role in the etiology of Paget's disease. They found a high incidence of tallness in the family, with diabetes mellitus and obesity. They suggested that the pituitary gland is primarily and the parathyroid secondarily concerned. Tall, obese persons, especially with a family history of diabetes, should not intermarry. Dickson, Camp and Ghormley (1945), in a full review of Paget's disease, cite a family in which the patient's mother, brother, maternal grandmother and great-grandmother and one aunt were affected. In a pair of MZ twins the tibia was involved, but the disease is most frequent in the pelvis. Osteoporosis circumscripta is an early manifestation.

Van Bogaert (1933) described a family with Paget's disease and chorioretinitis pigmentosa. There were six cases of retinitis and four of Paget's disease in four generations, three individuals having both (Fig. 174). Both were transmitted as irregular dominants. The osteitis developed first, the retinitis pigmentosa showing later and leading to blindness. Camurati (1922) described a family with osteitis deformans in the lower limbs only. There were eleven cases (all male) in four generations. Williams (1929), in a study of human paleopathology in which many diseased conditions were recorded in Egyptian mummies and in Neolithic skeletons, found that symmetrical *osteoporosis of the skull* was common in American Indians of the area where maize was cultivated as the chief food. This is known as *Schüller's disease*, the bone being porous. It is associated with lack of vitamins, old age, toxic goitre and various other conditions, but there is no evidence that it is inherited as such. Hooton (1930) found it in 3.3 per cent of crania (especially infants and children) from the Pecos Pueblo, and Ford, Quimby and Snow (1945) find it in skulls from an early Indian culture on the Lower Mississippi.

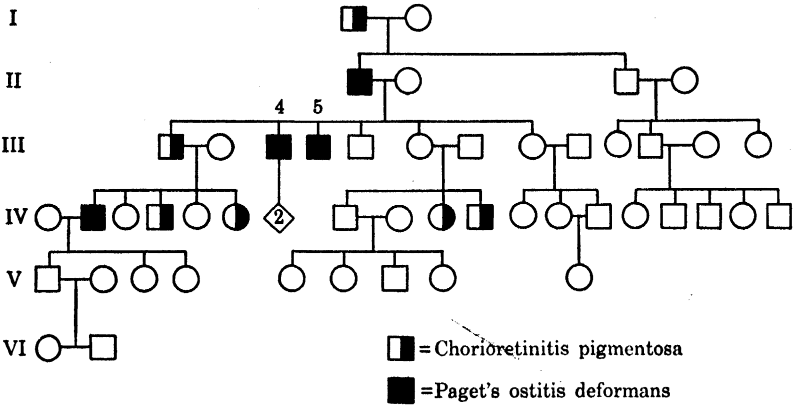

Fig. 174. Pedigree of Dutch family with osteitis deformans and retinitis pigmentosa. (After van Bogaert)

In a recessive lethal mutation in rats (Grüneberg, 1938) the most fundamental of various pleiotropic effects was an anomaly of the cartilage. Hyperplasia of the ribs and the cartilaginous rings of the trachea leads to distension (emphysema) of the lungs, from which the rats die in a week to a month. Fell and Grüneberg (1939) showed by tissue cultures that some of the cartilage cells are abnormal, the gene thus acting directly on chondrogenic cells to produce abnormal cartilage.

Nutrition and living conditions are known to play an important and probably essential part in the production of *rickets.* It is well known that lack of vitamin D will produce rickets and that damp living conditions and lack of sunlight favor it. But among families living in equally unfavorable conditions, one will be much more affected than another. The rachitic diathesis is evidently inherited. Ziesch (1925) made a study of rachitic families in Munich in 1916–23. Among 230 families, in 5 cases both parents had had rickets, in 21 the father only, in 34 the mother only. In 82 cases rickets was excluded in both parents and 88 cases were doubtful. In 12 pedigrees, one extending to four generations, the rachitic diathesis appears to be inherited as an irregular dominant with occasional skips.

Smith (1934) described a remarkable family in Illinois suffering from *ulceration of the soles of the feet* (Fig. 175), accompanied by anaesthesia and destruction of bones in the foot by splintering. The disease might be diagnosed as leprosy, but it is confined to the foot soles, though certain phalanges of the toes may also be lost. In this family a father, his two half-brothers and three sons were affected. The condition is confined to males, but there is no evidence that females transmit. The gene appears to be in the Y-chromosome. The youngest case described was sixteen years of age, and the sons appear to be normal up to puberty. It is not stated whether the two normal sons in generation III are younger, but if they developed the condition later it would be proof of another gene in the Y.

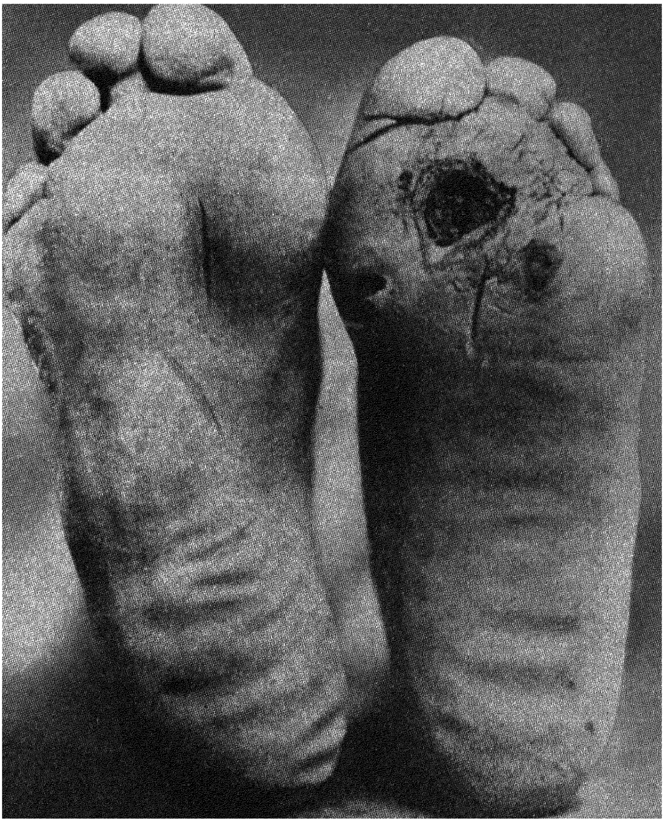

Fig. 175. Inherited ulceration of the soles of the feet. (After Smith)

Tocantins and Reimann (1939) published another remarkable pedigree of *ulcers of the feet.* The condition was dominant, with 8 cases (6♂ 2♀) in three generations. There were skin and sensory changes in three others, and harelip and cleft palate were also dominant with five cases in the same pedigree. In two brothers the lesions began at about seventeen with a small blister on the sole of one foot, soon followed by a blister on the other sole. Ulcers form in a month, the metatarsals and phalanges becoming deformed and destroyed by the discharge of spicules of bone from the ulcers. There was cyanosis of the toes and in some cases amputations of the feet were necessary.

The syndrome is attributed to an organized dysgenesis of the central nervous system of the type described by Fuchs in 1909 under the term *myelodysplasia.* Other families are described in Chapter XXIII under syringomyelia.

The *torus palatinus* is typically a boss at the back of the hard palate in the midline, but is variable and frequently extends forward as a ridge. Stieda produced a monograph on this structure in 1891, and Godlee (1909) recorded later observations. He found it in mother and daughter, and in two sisters of another family. It occurs in all races, but statements regarding its frequency do not agree. It was found in 56.3 per cent of one lot of 229 Peruvian skulls. According to Lissauer it has a high frequency in Lapps and the East Baltic. The frequency appears to be high in Ainu and low in Negroes. It is not pathological and is apparently not found in gorillas, chimpanzees or lemurs. Lasker (1945) finds it in 30 per cent of living Chinese, usually small; also in a Cantonese family in mother, daughter and son, not in the father; and in five pairs of brothers.

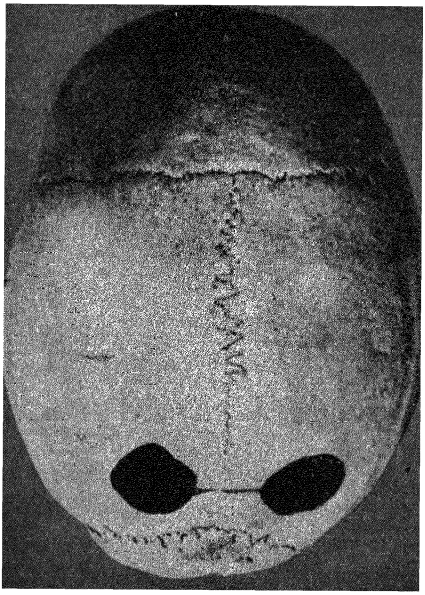

Fig. 176. Inherited openings in the parietal bones. (After Goldsmith) (From the *J. of Heredity*)

Fenestrae parietales symmetricae is probably the best name for a condition (Fig. 176) in which there are two large openings in the parietal bones, like eyes in the back of the head. They have also been called the *Catlin mark,* from an American family in which they occur, and there has been much difference of opinion as to whether they represent enormously enlarged parietal foramina. Normally the parietal bone frequently shows near its upper posterior angle a pinhole 1 mm. in diameter, through which a vein passes. It is very often missing, sometimes double and occupies roughly the position of these fenestrae. It is stated that foramina may be present along with the fenestrae, and that a large transverse fissure normally ossifies so that the foramina are formed. Hence it seems probable that, as Goldsmith (1941) contends, the foramina and fenestrae are separate structures with independent genetical determination.

Grieg (1897) found a parietal foramen in 70.3 per cent of 670 skulls; Cave found it in 67 per cent of 100 ancient Egyptian skulls, bilateral in 30 per cent. Modern Egyptians show essentially the same frequency. In 4228 skulls from various sources, Grieg (1917) found that 62.4 per cent had the foramen. Hence it is a usual feature of the skull, and its frequency is remarkably constant in different races. Stallworthy (1932) found it in 75.5 per cent of 310 Maori and Moriori skulls, bilateral in 29 per cent.

The fenestrae are generally about 2 cm. in diameter but may be 3 × 5 cm. They are frequently preceded by a single large opening which becomes divided down the middle. In anatomical museums, skulls with these large openings were observed over 150 years ago, and Lobstein described a case in 1772. They are symmetrical defects in the parietal bones, behind the crown and near the junction of the middle and posterior thirds of the sagittal suture. In the living head they are covered with skin and dura mater, but are clearly shown by X rays. There are no clinical symptoms. Grieg (1892) observed the first case in the living in 1889. Later (Grieg, 1917) the same condition was observed in the brother. He refers to a case in 1707.

Symmers (1895) described a case in a man of forty who died of pneumonia. His father had the same condition. Early instances were also recorded in France, and in 1932 there were about forty-six on record. Grieg (1927) discussed the subject more fully and described a case in a Negro skull and another in a female Mongolian imbecile. In one, only the right opening was present, displaced mesially. Stibbe (1929) described a Patagonian skull with small parietal fenestrae and extreme frontal shallowness, Stallworthy (1932) a Maori skull with fenestrae only 8 × 5 mm. and 7 × 7 mm. respectively. Ellis (1938) describes a male infant with two openings 2–3 cm. in diameter. The father was normal, but the mother had two flattened areas at this place in the skull. He cites Caussade, Niemann and Mariot (1937) who describe nine cases in three generations of a family.

Skulls with these openings are found in the collections at Edinburgh and Washington. Pepper and Pendergrass (1936), from whom the full literature may be obtained, described a white family with 9 cases (4♂ 5♀) in four generations, strictly dominant, and a Negro family with five cases in three generations. They report such a skull in the United States National Museum from an Indian burial mound at Palo Alto, California. Such skull openings have sometimes been regarded as the results of prehistoric trephining, but true cases of primitive surgery are distinguishable by the character of the free edge. Moreover, it is improbable that primitive man would make symmetrical paired openings such as these. It is evident that this mutation has been occurring in different races for thousands of years. Hauck's (1942) family has seven cases. Goldsmith (1945) believes that many supposed cases of trepanation in skulls from archaeological sites really represent this hereditary anomaly.

Parkes Weber (1935) cites cases from Egyptian mummies, and others in which there are symmetrical ovoid areas of *extreme thinness in the parietal bones.* He describes a case of "large parietal foramina" in a boy, his mother and one of her sisters.

Much the most extensive pedigree of the skull openings was published by Goldsmith (1922) of the Catlin family with 16 cases (9♂ 7♀) in five generations. It is clearly dominant, but with three skips and the sexes are equally affected. Voigt (1937) described a family with several cases, combined with other skeletal defects, including spina bifida occulta. He reported forty-five previous cases, mostly observed on the living. Halbertsma (1940) described a Dutch family with five or six cases in three generations, again dominant. One female child at four weeks showed a T-shaped opening in the back of the skull. At sixteen months the transverse part is separate from the vertical dumbbell-shaped opening below, and still later the horizontal part was divided medianly into two. Goldsmith (1941) deals with the literature of the subject. In some families there are associated abnormalities and he records the case of a Mongolian imbecile infant with two large fenestrae, and refers to other observations which show that the defect sometimes begins in infants as a long transverse opening which later divides into two. Its original form may then be elongated, T-shaped or in two separate circular windows.

Cockayne (1933) contends (p. 314) that this condition is really a form of *aplasia cutis congenita* or imperfect skin formation with a circular area of hairless skin at birth over the posterior fontanelle of two such areas lying side by side. He thinks that Goldsmith's photograph shows the overlying scalp to be hairless. If hairless areas were present in the adult scalp over the fenestrae they would surely have been observed and noted, at least in the men. Goldsmith speaks of an "elongated concavity" remaining in the "median septum." It is not stated to be hairless, and in the photograph the scalp and hair appear to be normal in the regions over the fenestrae while the depressed line over the median septum is clearly shown.

The *Inca bone,* a triangular bone in the occipital region of the skull, is found in all races but is said to be most frequent in the Incas of Peru. Matthews (1889) found six cases among eighty-eight skulls of Pueblo Indians in Arizona (6.8 per cent). Records from Australians, Tasmanians and Caucasians indicate frequencies of 0.64 per cent, 1.2 per cent and 6.1 per cent respectively. It is rarely perfect in Caucasians and there is no evidence as to how it is inherited. It is present in some Sinanthropus skulls. Sergi (1886) gives figures of its variations. An oblique suture dividing the *malar bone* into two may reach a frequency of 40 per cent in Japanese and 9 per cent in Europeans (Deniker, 1913).

By X-raying the *sella turcica* in five hundred individuals, Camp (1926) found it oval in 58 per cent, round in 24 per cent and flat in 17 per cent. Gordon and Bell observed that in children the round form predominated. The clinoid processes (anterior, posterior and middle) also vary in shape. Camp found that in 5 per cent of cases they unite to form a bridge. Snyder and Blank (1944), by X-raying 125 individuals, found 5 cases of bridged sella. They were all in three generations of one family, inheritance dominant. The condition appears to have no clinical significance in this family, although one suffered from migraine. Other studies suggest that a bridged sella is more frequent in pycnic individuals; it was present in all affected members of a family with the Laurence-Moon-Biedl syndrome in three generations; and in other families there is evidence of its association with hereditary metabolic and nervous disturbances.

Dillon and Gourevitch (1934) made a study of the *nasal sinuses, mastoid processes* and the size and form of the sella turcica in twins. From comparison of 11 MZ and about 13 DZ pairs they conclude that differences in the sella are chiefly genotypic, while in regard to the nasal sinuses and the mastoid processes paratypic factors predominate. In a further study of shape of the sella turcica, Snyder and Blank (1945) have X-rayed 100 persons in 24 families. They find 50 per cent oval, 41 per cent round, 9 per cent flat. From comparison of parents with children they suggest that Mendelian factors are concerned in the shape determination. In two families a small sella was found in one parent and in some of the children.

The degree of *pneumatization of the mastoid* is known to vary widely. Dahlberg and Diamant (1945) have measured the size of these cells or chambers from X-ray photographs of individuals. They find that chronic otitis occurs only in those with small chambers in the bone. From a study of 301 children and their parents, as well as 24 MZ and 44 DZ twins, they conclude that while environment has an effect on chamber size, yet the genes for small chambers predispose the individual to otitis.

Non-pathological *thinness of the parietal bones* is a well-recognized condition. Grieg (1926) summarized earlier cases. Camp and Nash (1944) cite 119 cases, usually bilateral (80 ♂ 39 ♀), finding a frequency of 1 in 217 heads X-rayed, with a mean age of over fifty years. Carrière found an incidence of 1 in 406. It has been observed in Maori, Moriori, Egyptians and Singhalese. Wilson (1944) describes a case in a Chinese and cites the literature. It is evidently a congenital defect in many cases, and whether it can develop as a senile condition is doubtful.

The *foramen magnum* varies in rats from pentagonal to oblong (Keeler, 1941). Multiple genes are involved, with oblong as recessive.

The *genial tubercles* or spines, on the inside of the mandible in the midline can be palpated in the living subject. Thomson (1916) observed them in various races and shows that they have no connection with speech. This area, to which the genial muscles are attached, may be smooth or the two superior spines may be replaced by two little pits. These pits may coalesce, forming a depression or rarely a fossa. All these conditions serve to increase the attachment area. Their inheritance could probably be studied in the living.

Parted frontals with cerebral hernia is an inherited condition in cattle, pigs, mice and some breeds of fowls. Shaw (1938) found it as a recessive lethal in Holstein-Friesian cattle. In pigs there are indications that the abnormal young are resorbed before birth. Keeler (1933) found in a wild house mouse a simple recessive gene producing *interfrontal*, a narrow bone between the anterior part of the frontals. Dalquest and Scheffer (1944) have observed a similar condition (internasal bone) as a local mutation in a species of pocket gopher.

The *metopic fontanelle* is a developmental abnormality of the skull. In the human foetus of less than five months the frontal arm of the bregmatic fontanelle reaches forward below a line connecting the frontal tuberosities. Its lowest portion, the metopic fontanelle, persists until birth and early infancy in 15 per cent of children. Schultz (1929) describes these conditions and points out that the metopic fissure remains in various mammals and in human races. In North Chinese the frequency of this fontanelle is 9.1 per cent, in Japanese 6.2 per cent, in Filipinos 0.3 per cent. It is not due to increased intracranial pressure, but is probably the result of a hereditary tendency to arrested development in the lower mid-sagittal region of the frontal bones.

Depression of the obelion (the region of the lambda at the line of fusion of the occipital and parietal bones) at the back of the skull is inherited in two pedigrees. Milles (1928) cited a family with 16 cases (10 ♂ 6 ♀) in four generations, in which the depression varied in depth, the skull being shaped like a helmet at the back. She cites Stocks' family with 12 cases (8 ♂ 4 ♀) in four generations. The condition is dominant, but the sibships numbered 11 affected : 24 normal. Goodman (1915) described two children of the same mother who had a depression in the temporal region. One afterwards outgrew it. Usually the parietal bones, but sometimes the temporal and occipital, are affected.

In an estimate of the frequency of *tower skull*, Jensch (1942) found six cases among 1658 polyclinic patients in Germany, but none in the normal population. He calculated the frequency to be 0.2 per cent in the psychiatric population. A total of 82 probands were found, of whom 9 (11 per cent) were twins, indicating an influence of crowded conditions *in utero*. Ten cases showed inheritance, but the manner of inheritance is not clear. Sixty-six came from psychiatric families and in 75 per cent there were other dysplasias besides tower skull.

Keller (1941) describes two cases of *spherocephaly* in rabbits and discusses problems of development with special reference to Spemann's organizers. The spherocephaly arose from derangement of the head organizers, so that the brain and sense organs developed under reduced influence of these organizers from the earliest stages. The genesis of typical head-malformations in the higher vertebrates arises from similar derangements in the determination mechanism, the normal development of the brain and sense organs being dependent on the formation of normal head-organizers.

That various conditions can produce *scoliasis* (curvature of the spine) is well known. I have seen the records of a pair of identical twins, one of whom developed scoliasis which made considerable changes in her physique. It is not so well known that scoliasis can be inherited. Garland (1934) records a family in which the inheritance is dominant with one possible skip in five generations. There were 9 cases (5 ♂ 4 ♀), the sibships numbering 8 or 9 affected : 10 normal. The pattern of the deformity was remarkably constant, with resulting distortion of the thorax. Radiograms show no structural defect in the vertebrae or intervertebral discs and there was no disease of the nervous system. This appears to be the first pedigree of the Mendelian inheritance of scoliasis, but Tubby in 1896 (*Deformities*, p. 104) considered heredity to be common in scoliasis and cites two families, each with several affected members. Rutherford (1934) also recorded scoliasis in grandmother, mother and daughter. There was no rickets, and generations I and II lived in the country, generation III (6 children, 5 unaffected) in the city.

Scoliasis often appears as a secondary effect of other deforming genes. In a pedigree of Weissenberg (1928), a Jewish family in the Ukraine showed four cases of scoliasis in two generations. The vertebral column was bent to the right and the inheritance appears to be that of a dominant with low penetrance.

Stone and Henriques (1917) described (*a*) absence of coccyx, as a variation, (*b*) short coccyx, (*c*) absence of the condyles of the right femur at birth. The last was due to syphilis and developed normally after treatment.

Variations in the Vertebral Column

Many variations in the vertebrae have long been known. In an anatomical study of the vertebral columns of eighty-two Bantu, for example, a remarkable abundance of abnormalities was found by Shore (1930). Variations at the lumbo-sacral junction were less common than in Australian aborigines but more common than in Europeans. In seventeen columns the thirtieth vertebra was added to the sacrum — a higher frequency than in Europeans. Spina bifida was present in fifteen columns (18 per cent) and spinous processes were absent in sixteen cases. Other abnormalities were cervical ribs, abnormal lumbar transverse processes and division of the lamina.

Recent work, using X-ray photographs, has made it possible to group these variations together from the point of view of inheritance. Kühne (1931) studied such records of the vertebral column for 10,000 persons and especially for 23 families containing 121 persons. In the vertebral column no two vertebrae are exactly alike and the "normal" number may range from 32 to 37. As the vertebrae are formed by segmentation of an originally continuous structure, they may be expected to show rhythmical waves of change from one end of the column to the other. The whole column is in this sense a unit of continuous change, with more marked breaks at the four critical points. The column segments into somites with metameric muscles and spinal nerves. When the early embryonic processes of the nerve plexus for the arms and legs appear, this involves changes in the vertebrae concerned. Generally the condition is

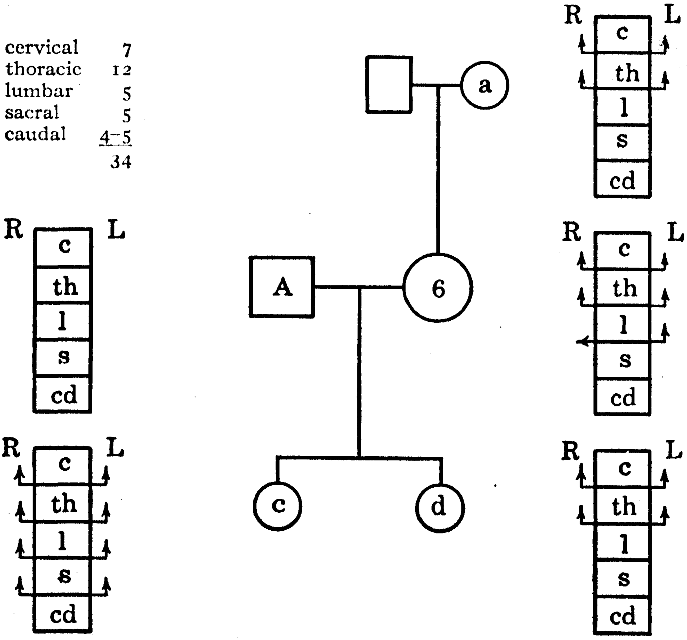

Fig. 177. Diagrams of the vertebral columns in a family. (After Kühne)

It is found that the significant variations occur at the border lines between one type of vertebra and the next. As shown in Fig. 177, the various types of vertebrae are determined mainly (as regards their variations) by their various attachments. These are represented by arrows on the right or left side at the four border lines. If, for instance, the first thoracic vertebra shows (on one or both sides) certain features of a cervical vertebra, then the variation at that point is cranialward. If, on the contrary, the last thoracic shows features of a lumbar, then the variation is caudalward. In this way all variations at the four border lines can be classed as cranialward (↑) or caudalward (↓) variations. Generally in one spinal column all the variations will be in one direction or the other, although there are exceptions to this.

Thus in Fig. 177, the grandmother (*a*) showed a tendency to shift the cervico-thoracic boundary in the cranial direction, and a similar tendency to shift the thoraco-lumbar border in the same direction, as shown by the reduction of the ribs on the nineteenth vertebra. The daughter shows the same tendency at the cervico-thoracic, the thoracico-lumbar and on the left side at the lumbo-sacral border. Her husband was "normal," showing neither cranialward nor caudalward shifts. Of their two daughters, *c* shows a cranialward shift at all four border lines, while *d* shows the same at the two upper points. The cranialward variation in *d* is shown at the cervico-thoracic border by the presence of a large neck rib, and at the thoracico-lumbar border by strong reduction of the last rib, as in the grandmother. According to Rosenberg, in the human embryo the future first lumbar vertebra normally forms a rib, which is then absorbed, leaving a transverse process. The last cervical vertebra also forms a rib-like structure, which is free until late childhood when it unites with the vertebra to become a transverse process.

Kühne found that the inheritance of all these variations could be explained in all families by the assumption of one pair of alleles, **Cr** representing the tendency to cranialward variations and **cr** the caudalward tendency, determined at the time of the original segmentation. This apparently formal explanation nevertheless links together a vast amount of detailed observation of inheritance of variations in the vertebral column. Every individual will be either **CrCr, Crcr** or **crcr** as regards his vertebral constitution. **Cr** (↑) is dominant to **cr** (↓), but shows incomplete penetrance. What is regarded as the normal condition is thus a balance between these two genic effects, so that about 50 per cent of "normal" individuals will be **crcr** and about 50 per cent **CrCr** or **Crcr.** The intensity of the cranialward variations is greater in homozygous **CrCr** than in **Crcr** individuals. Kühne's pedigrees also show that most "normals" may be **Crcr** and that these heterozygotes show less expressivity than the homozygous **CrCr.**

Furthermore, the homozygous recessive, **crcr,** shows higher penetrance than **Crcr,** and no "normal" (non-penetrating) **crcr** individual has been found.

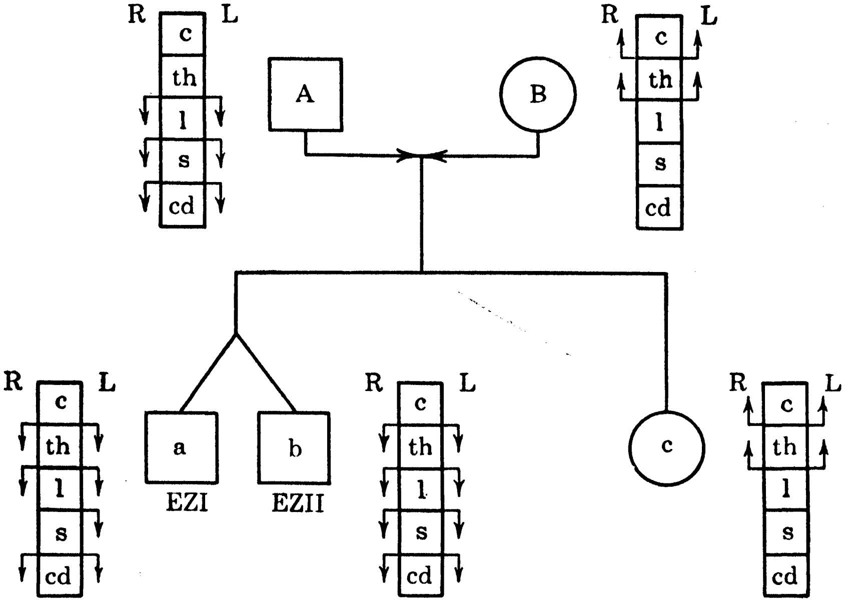

Fig. 178. Diagram of the vertebral columns in another family. (After Kühne)

In a later paper (Kühne, 1936) these views are supported by a full study of 108 pairs of twins, 53 of them monozygotic. One case may be taken as an example of this study. Figure 178 is a diagram of a family, showing the caudalward (**crcr**) variations of the father, the mother being **Crcr.** The MZ twins are **crcr** like the father and the daughter is **Crcr** like the mother. The twins are alike except for the failure of the caudalward tendency to appear on the right side at the lumbo-sacral border in one twin. The exact vertebral conditions at the different border lines in both twins are shown in Fig. 179, the abnormal points being shaded. The main features, all pointing caudalward, are (1) in both twins the transverse processes on the seventh cervical are definitely small, whereas in a cranialward variation they would form cervical ribs, (2) in vertebra XX (the first lumbar) a small pair of ribs 12 mm. long is present in one twin, (3) vertebra XXV on the lumbo-sacral border is definitely lumbar on both sides in one twin but is sacral on the right side in the other, (4) both twins show spina bifida occulta of vertebrae XXV and XXVI, (5) vertebra XXX is attached to the sacrum in both.

Through minimal expressivity or failure of penetrance of the allele a **Crcr** individual, or even possibly one who is **crcr,** may appear phenotypically normal. Unselected material in Berlin gave 58.5 per cent cranialward and 34.2 per cent caudalward variations. Dividing the 7.25 per cent "normal" among the other two gives a frequency of 63.1 per cent ↑ and 36.9 per cent ↓, or roughly nearly 2 : 1. Of the 52 pairs of MZ twins, 29 are ↑ ↑, 19 ↓ ↓. In one pair, one twin was normal, the other showed cranialward variation. The normal one was a latent ↑ showing lack of penetrance. Thus in the identical twins there was nearly 100 per cent concordance, while in 55 pairs of DZ twins about three-quarters showed concordance. In homozygotes the expressivity is increased about 50 per cent over that of heterozygotes.

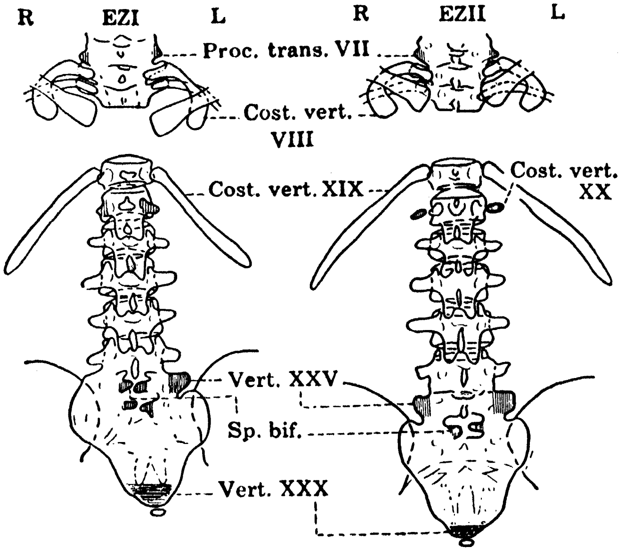

Fig. 179. Drawing of the vertebral columns of the twins in Fig. 178. (After Kühne)

The so-called normal condition thus arises from failure of penetrance, which is equal for both cranialward and caudalward variations. Only genetic analysis can determine to which group a particular normal belongs. The genes **Cr** and **cr** are also polyphanic (or pleiotropic), affecting not only the vertebral column but the peripheral nervous system, musculature, blood vessels and most of the organs in the thorax and abdomen, so it would be impossible to find a more fundamental genic difference. **Cr** can be regarded as an accelerator and **cr** as a retarder of development. The origin and morphological significance of all this variability can thus be explained by the pre- and postnatal ontogeny of the regional boundaries of the vertebral column.

Steiniger (1938), in a further study of vertebral columns and tail reduction in vertebrates, points out that the normal number of presacral vertebrae is

24. It may be 23 in the cranialward variation (**Cr**) and 25 in the caudalward (**cr**). He finds racial differences in the frequency of these genes, **cr** being stated to be more common than **Cr** in Czechs, Russians and Japanese. He goes further, and assumes that the tendencies represented by **Cr** and **cr** are determined by biochemical (hormonal) differences in development which are perhaps postnatal in origin. **Cr** and **cr** are fundamentally concerned in determining the segmental structure of the whole body. He suggests that **Cr** generally produces the broad (eurysomic) type of body build and **cr** the slender leptosomic type, even determining the correlation found between body build and psychic condition. Whether the theory will bear this added weight of hypothesis remains to be seen, but at any rate the simple assumption of one pair of genes is sufficient to account for all the cranialward and caudalward variations usually found in the human axial skeleton. Frede (1934) has applied the same principles to variation in the vertebral column of the rat, including variations in the brachial and the lumbo-sacral nerve plexus. Lanier (1944), applying Kühne's methods, found no difference in vertebral types between whites and Negroes. In 559 subjects, 1.1 per cent showed cervical ribs and 8.8 per cent lumbar ribs.

Green (1941) studied variations of the vertebral column in different strains of mice, involving extra ribs at the thoraco-lumbar border. These variations are found in many mammals and probably occur in all. Inbred mice stocks were found to differ in their skeletal types, about 50 per cent of the factors acting over the thoraco-lumbar and lumbo-sacral borders, the rest having a more restricted action. Green (1939) crossed two families of rabbits, one having twelve pairs and the other thirteen pairs of ribs. In the F_1 about 84 per cent had twelve pairs. The F_2 and back-crosses gave results closely resembling single factor segregation. Another back-cross gave less definite results. Extra presacral vertebrae, the number of ventral spinous processes and of sternebrae (segments of the sternum) are associated variations which may all be determined by a complex of genes. In a further study of the vertebral column in rabbits, Sawin (1945) finds evidence in one family of a gene producing extra skeletal units at the thoraco-lumbar and the lumbo-sacral borders. In another family the inherited differences were at the thoraco-lumbar border only, and in a third at the lumbo-sacral border only. These inherited variations are produced by genes affecting localized embryonic areas and the number of such factors may be large. By a study of rabbit embryos belonging to two strains which differ in rib number, Baumgartner (1945) finds a difference in the time of onset of the ossification centres governed by one pair of genes, difference in rate of ossification by several, and regional differences controlled by a number of other genes.

Vertebra plana is an apparently rare condition described by Calvé in 1925. Usually a single vertebra is affected. Beginning in early childhood, necrosis of the vertebral body takes place in about two months. Then it slowly regenerates over a period of eight years or more. Only about seventeen cases have been certainly recorded. Heredity has apparently not been suggested as a cause, but it is difficult to imagine any other which would produce such a circumscribed effect. Massaro

(1945) describes a case with skiagrams and references to the literature.

Spina bifida is a well-known defect of the spinal column, but little has been known of its inheritance. Frogs' embryos not infrequently show spina bifida, and as early as 1894 Morgan (1903) produced this condition by treating the fertilized eggs with lithium chloride. Hertwig (1896) found that 0.7 per cent sodium chloride delayed gastrulation twenty-four hours, leading to a duplication of what we would now call the *organizer*, so that all the embryos showed spina bifida. Baldwin (1915) afterward produced spina bifida invariably in frog embryos by killing with ultraviolet light a small area of the yolk hemisphere or of the equatorial region in the fertilized egg. As a result, the backward growth of the dorsal lip of the blastopore is retarded and the two lateral halves of the neural tube fail to fuse. Thus very different physical and chemical agencies can produce the same result. How the gene for spina bifida produces its effect is unknown.

The anatomy of this condition is considered in some detail by Keiller (1922). Myers (1930) described twin girls and another child, all with spina bifida, in one sibship, a fourth child being normal. Shamburov (1932) described twenty-three cases, each with a short pedigree of two generations. He finds that spina bifida occulta is the heterozygous condition, of which sp. bifida aperta (or sp. bif. cystica) is the homozygous counterpart. It is generally fatal in infancy. The occulta condition may be due to irregular ossification of the vertebral arches or dysplasia of the spinal cord, generally in association with dysplasia of the brain.

It has been connected theoretically with the assumption of an erect position and with the loss of a caudal appendage. This does not explain the cases accompanied by nervous derangement which render the bearer an invalid. The most probable view is that failure to close the bony canal (which is normally completed at about seven years) is closely related to irregularity in the formation and closure of the medullary tube. This accounts for the accompanying defects in the nervous system. The primary defect can be sought in the nervous system, spina bifida being an expression of a local (sacral) trophic insufficiency. Galloway (in Fouché 1937) finds spina bifida remarkably frequent in South African Negroes and regards the condition as a reflex of their hybrid constitution.

In childhood, incomplete arches of the lumbar vertebrae are frequent and may even be as high as 50 per cent. Spina bifida is more common in males than females. The heredity is thus partly sex-limited and is under the influence of other hereditary factors. Its occurrence can be influenced both by environmental and internal factors. The condition is frequently stated to be accompanied by *enuresis nocturna* in childhood, but according to Morrison (1944) it has been proved that there is no relation between spina bifida occulta and bed wetting. The inheritance of the latter condition was studied by Petrovsky (1934). Frary (1935) concludes from many short pedigrees that it is a simple recessive. She studied 113 ♂ 81 ♀ cases of ages three to eighteen and over twenty years, but mostly between six and twelve years. Six family trees are given. The severe type of enuresis was present in a pair of MZ ♀ twins thirteen years of age. Environmental influences, especially the attitude and intelligence of the parents, are considered secondary but important. From a series of cases of narrowing of the spinal canal, Sarpyener (1945) concludes that it is responsible for many cases of enuresis as well as clubfoot, spastic and flaccid paralysis, due to compression of the spinal cord. Shulman (1942) records two successive sibs with spina bifida cystica and meningocele in one family. The frequency of spina bifida cystica has been estimated at 1 in 1000 births.

Estimates of the frequency of spina bifida range from 3.5 to 24 per cent, Curtius finding 17.3 per cent while Schwarzweller (1937) X-rayed 1000 vertebral columns and found 144 cases, or 14.4 per cent. Claussen (1939) states that spina bifida aperta is found in *ca.* 1 newborn baby per 1000 and sp. b. occulta in *ca.* 50 per cent of newborn and 16 per cent of adults. In Schamburow's X-ray studies of families he found 70 persons affected out of 119, or over 50 per cent. The probands were found by X-raying persons in hospital with lumbo-ischial pain. Saunders (1943) describes a case of combined *anterior and posterior spina bifida* and classifies thirty-seven cases. This condition is ascribed to a cleft notochord accompanied by endo-ectodermal adhesion.

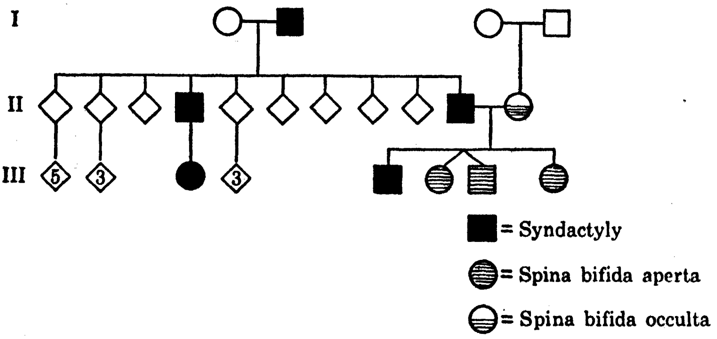

Fig. 180. Pedigree of spina bifida and syndactyly, modified. (After Weidenmüller)

A family (Fig. 180) in which spina bifida was present with syndactyly was studied by Weidenmüller (1936). There were four cases of spina bifida and five of syndactyly in three generations. The latter was a simple dominant and consisted in the webbing of toes II and III. Spina bifida occulta was present in II. 11, spina bifida cystica thoracica in III. 7, acrania with hemicephaly, spina bifida cystica and hydrocephalus internus in the twin III. 6, and partial rachischisis in III. 8, together with clubfeet and hydrocephalus internus. From the work of Bagg and of Bonnevie (*q.v.*) on inherited bleb formation in X-rayed mice, Engel concludes that various similar defects in man arise as bleb disorders. A recent discussion will be found in Hobbs (1944). He cites familial cases of spina bifida associated with *lacunar skull* and of spina bifida with anencephaly and hexadactyly.

By *rachischisis* is understood congenital fission of the spinal column (i.e., the failure of the axial skeleton to close), spina bifida being a terminal form of rachischisis. The various types of failure to close the spinal column are regarded as aspects of the *status dysraphicus* and were attributed by Weidenmüller in the above family to alcoholism. The closure which fails in rachischisis normally takes place in the second or third week *in utero.* The conditions observed show considerable variation, and while the occulta and aperta forms of spina bifida appear to represent respectively the heterozygous and homozygous forms of sacral spina bifida, it is not yet clear whether the cystica form represents the same gene or an allele in homozygous condition. The earlier failure represented by rachischisis may be determined by another allelic gene. In a further discussion of these conditions, Waldmann (1938) cites four other small pedigrees and points out that they are often accompanied by other inhibitions of development and growth of the mesodermal skin-muscle plate in the region of the back and the abdomen, resulting in umbilical hernia.

Schwarzweller (1937) has studied the relation of spina bifida, scoliasis, synostoses and *high shoulder blade* (Sprengel's deformity). In the last condition there is dislocation of the scapula by retraction of the levator anguli and the upper part of the cucullaris muscle. Eulenberg described three cases in 1863, Grieg (1924) discussed the anatomy of congenital high shoulder blade and brevicollis, and Aschner (1928) concluded that congenital high shoulder blade is an inherited recessive pathological condition. It is nearly always accompanied by other hereditary defects belonging almost exclusively to the mesoderm and is especially common with the above-mentioned malformations of the spinal column. Schwarzweller thinks they are all determined by the same hereditary gene. In nine families with *scoliasis*, in which 43 persons were X-rayed, he found 15 cases of spina bifida, 4 of synostoses, 25 of scoliasis, and 8 of other vertebral anomalies, 6 also having high shoulder blade on one side and 3 on both sides. In one family, a brother and sister had high shoulder blade on both sides with cervical vertebral synostoses. The frequency of spina bifida in these families was 34.9 per cent, against 15.8 per cent in the general population. Synostoses generally occur with a frequency of 1 in 1050. Gottesleben (1927) has a pedigree of high shoulder blade on one or both sides, with 9 cases (4♂ 5♀) in three generations, the inheritance strictly dominant, sibships 9 affected : 11 normal. Braun (1939) records a pair of MZ female twins, both having scoliasis and a foot deformity, one only with luxation of one femur.

Bonnevie (1936) described a recessive mutation in mice, causing a cleft in the neural tube, such as spina bifida, rachischisis or cranioschisis. The primary effect was probably a delay in the separation of the germ layers. This delayed the development of the mesoderm, while the ectodermal derivatives (neural tube and brain) grew faster and became contorted. From this evidence, all the similar conditions in man may be due to a single gene.

Scapular Shape

Variation in scapular shape has been much studied, but its interpretation is still somewhat controversial. Dwight recognized in 1887 that the vertebral border below the scapular spine might be straight, convex or concave. Graves (1910) showed that these differences could be recognized in the living, and classed the straight and concave borders together as scaphoid, in contrast to the convex. He also found the scaphoid type in syphilitic children. In later studies (Graves, 1921) these three scapular types were found in many modern and ancient racial groups. The straight and concave were found to have many features in common and to make up nearly half of the dissecting-room material with an average age of fifty years.

The scapula begins to ossify toward the end of the second foetal month but it only reaches maturity in the twenty-fifth year of life. It is regarded as the most variable large bone in the human body. In foetal life it is always convex (Fig. 181a) and almost hemispherical. According to Hrdlička (1942b), differentiation into other forms begins about the fifth month, and later the straight and concave forms appear. Figure 181a shows skiagraphs of the scapulae of six foetuses, 280 days gestation. The original convex form is clear, as well as the later form, which may be convex, straight or concave in different combinations. Figure 181b shows the various scapular type combinations in six adult individuals. From a study of age changes in 139 pairs of scapulae of white males ranging from eighteen to eighty-eight years of age, and other studies of white and negroid scapulae at the Hamann Museum, Graves (1922) concluded that ossification and atrophic processes both occurred in the scapula during this period. From further studies which included 18,457 living and 2772 dead persons of various ages, Graves (1924) concluded that each scapular type was hereditarily determined, and by observations on families in three generations he found that the type of scapula usually depended on the parental types but that occasional disease might alter such inheritance. He developed the *age-incidence principle* of investigation and concluded that, on the whole, those with a convex scapula were longer lived than those with straight or concave scapulae. The frequency of the convex type was found to increase while the straight and concave types decrease in successive age periods from birth to old age. Such a principle, if inherited differences are involved, would be important as showing a selective process at work in favor of the convex scapula. This process, if long continued, should show a tendency to the elimination of the less favorable scapular types. The possibility that with age one scapular type changes into another was also considered; but the conclusion was reached (*a*) that the scaphoid does not change into the convex after about the tenth foetal week, and (*b*) that the scaphoid is more often found than the convex in the "plus-potentially sick, the

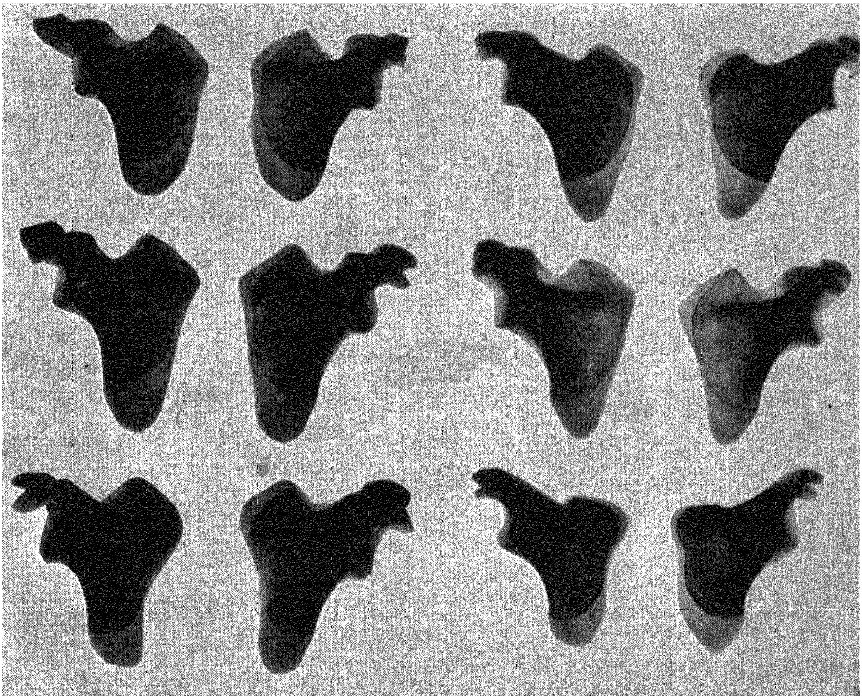

Fig. 181a. Skiagraphs of the scapulae of six foetuses. (Photo from Dr. W. W. Graves)

shorter-lived of the race." A particular scapular type was recognized as only a part of the individual's inheritance, and hence as a conditional and not an absolute index of constitution. This is also shown by the fact that any combination of the three scapular types can occur in one individual. Although the scapular types can be recognized in the living, no observations have yet been made, to follow the inheritance of any particular type through successive generations. It is possible that the genes determining scapular shape may have pleiotropic effects, and that selection acts on some of these rather than on the scapula itself.

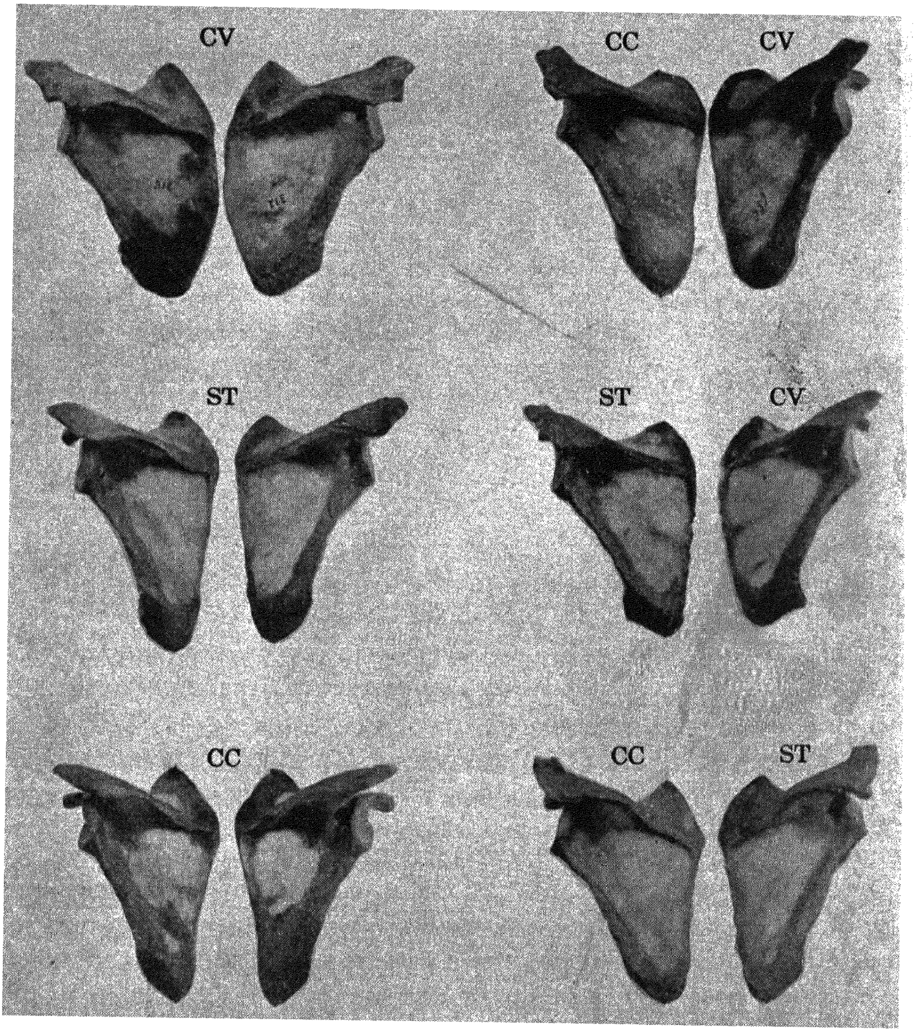

Fig. 181b. Scapulae of six adults. (Photo from Dr. W. W. Graves)

The statistics from various workers in the United States, Germany and Austria clearly show an increase in the age-incidence of the convex type of scapula. Extensive unpublished material kindly supplied by Dr. Graves shows large differences in incidence between school children and old people, but opinions differ as to whether this results from a selective process or from a functional transformation in the shape of the bone. In 3598 school children aged six to fifteen years, only 36.44 per cent were of convex type, while 2467 people from Old People's Homes, aged sixty to eighty, showed 67.45 per cent convex. It was also found (Graves, 1931) that when healthy groups, such as high-school and university students and soldiers, were compared with various sick groups (tuberculous, insane, feebleminded and prisoners), the corresponding age periods show from 1.25 to 2.25 times as many convex scapular types in the former as in the latter.

A study of 1200 mature scapulae shows that the concave and straight types have twelve or more other features in common, contrasting with the convex type. Similar types have been found not only in ancient and modern human stocks but in the gorilla, orang, chimpanzee, lemur, armadillo, bat, etc. The right and left are not, however, always of the same type, although all types are found in different occupations and in both sexes. Further statistics on the subject are given in Graves (1932). Tabulation of some 60,000 persons shows that scaphoid types predominate in the young, and convex types in the old. From the twelfth week to ten years there are *ca.* 20 per cent convex, at ages seventy up *ca.* 80 per cent convex. To prove that the shape of the vertebral border of the scapula is an inherited variation, however, requires family pedigree studies such as have not yet been made.

Frey (1924) controverted the conclusions of Graves. She first expressed the view that the size of the infraspinous process of the scapula is related to its function, being broader in men than women and in strong-muscled than in weak-muscled men, small in men of occupations requiring little strong movement and very broad in occupations using the attached muscles of the back. Regarding the vertebral margin, she found it generally straight or concave, but convex in occupations requiring little muscular effort. She regards the scapular shape as an adaptation, the vertebral margin especially not being completed until the twenty-fourth or twenty-fifth year. The scaphoid scapula is not, in her view, a sign of degeneracy, but depends on muscular development and occupation.

Kerr (1928) made observations on the scapulae of 546 Chinese of ages fifteen to seventy-eight, using palpation and X rays. He found that 47.2 per cent were convex, 35.4 per cent straight and 17.4 per cent concave, and he confirmed Graves in finding a definite decrease in the incidence of the scaphoid type in each succeeding decade of age. This was interpreted as a higher death rate among those with scaphoid scapula, but tuberculosis was found to be as frequent in persons with convex as with scaphoid scapulae.

Schultz (1930), in an extensive comparison of the skeletons of the higher primates, found that the scapula in gorillas was as variable as in man, both as regards the shape of the fossa supraspinata and the vertebral border, which may be convex, straight or concave. He finds the scaphoid types of scapula quite common in gorillas and disagrees with Frey's conclusion that scapular shape is entirely a result of functioning. The scapula of the mountain gorilla, *G. Beringei*, already differs from that of the lowland gorilla in infancy, the latter having a convex border as in the human foetus, while in *G. Beringei* the vertebral border has a characteristic irregular shape in all five adult specimens examined.

Hrdlička (1942), in a series of three papers, has surveyed the scapular variations, dealing particularly with American white, Negro, Indian, Eskimo and Aleut scapulae, as well as Egyptians and Pacific Blacks. He measured 3060 adult scapulae. His types 6, 1 and 3 correspond respectively with convex, straight and concave. He finds a larger proportion of type 1 (straight) in females, and slightly less of type 6. During the growing period all indices diminish with age, indicating that the scapula grows more in length than breadth; but in females it remains relatively broader, hence more infantile, and absolutely smaller in dimensions. He finds "no conclusive sign of the earlier elimination" of individuals having the concave type and regards this type as a normal more or less aplastic condition of the vertebral border due to less development of attached muscles, perhaps caused by weakness of these muscles or by some peculiarity of trophic innervation. He believes that, due to muscular demands, the concave type may change during life to nearly straight, but that in the less robust and active it may persist throughout life. He holds that the convex type (6) *decreases* steadily in frequency with age, but Graves' statistics appear to show the contrary. Hrdlička finds that the straight type increases while the concave type remains much the same. He agrees that the concave type, though it may disappear "within the life of the bone," may be due to "inherent causes."

Hrdlička also concludes that the great variability in the superior border of the scapula, in which the notch may be rounded or saddle-shaped, is related to muscular activity. In Eskimo and Alaskan scapulae he found eleven instances of a foramen piercing the flat body of the bone, in some cases bilateral. In a white baby, both scapulae showed no depression of the superior border, and in a Negro baby the scapulae lacked completely the superior angle as well as the superior border. Hrdlička found no significant racial differences in the scapula and concludes that the bone is almost entirely a muscular product, all its features changing with age.

In an extensive racial study of the scapula, Vallois (1932) finds the concave type characteristic of Europeans and rare in other races. He attributes the lesser frequency of this type in adults than adolescents to the development of an ossification centre at ages twenty to twenty-five years which causes the disappearance of the concavity.

From all the evidence, one may perhaps conclude that scapular types may be inherited and that the concave type stands apart from the others as an indication of constitutional weakness. That it can change functionally into the straight type is not proven by observation. Its manner of inheritance remains to be determined by studies of families and their development through three generations.

That diet may have some effect is shown by the work of Warkany and Nelson (1941), who found that when rat mothers are reared on a certain deficient diet the young show multiple skeletal abnormalities — shortening or absence of tibia, fibula, radius, ulna and bones of the feet; syndactyly, shortening of the mandible, fusion of ribs, and various deformities of sternum, maxilla, clavicle and scapula. In a further paper, Warkany (1944) shows that in rats various defects in the young result from a deficiency of vitamin A or D in the pregnant mother. Warkany, Nelson, and Schraffenberger (1943) find that the skeletal defects begin at the cartilaginous or precartilaginous stage. Lack of longitudinal and transverse cell divisions in the cartilage leads to reduction in the number of skeletal elements and to syndactyly and brachydactyly.

Funnel chest, cobbler's breast, pectus excavatum or Trichterbrust is an inherited condition which was formerly supposed to result from an occupation such as that of the cobbler stooping over his last. It was described by Bauhin in 1594 and consists in a depression of the lower end of the sternum, which may be congenital but usually arises later. It varies considerably and mild degrees of it are common. The depression of the sternum generally takes place gradually, and even when the heart is displaced and flattened there may be no symptoms or discomfort. In other cases palpitation and shortness of breath may result, but operation promptly relieves the symptoms.

Cases are described by Edeiken and Wolferth (1932). A lad of seventeen who was born with this hollow in his chest was described by Williams (1872). W. von Ebstein (1882) gave it the German name and reported five cases in the literature. Carr (1933) described the cardiac complications. Troisier and Monnerot-Dumaine (1930) produced two pedigrees of funnel thorax, with ten cases in four generations of dominant inheritance. In one family a short metacarpal was also inherited. Peiper (1922) first showed the dominant inheritance, with a family having 7 cases (4♂ 3♀) in three generations. Nowak (1938) gives twelve short pedigrees with 33 cases in all (20♂ 13♀), inheritance dominant but with three skips. In examining 30,000 Vienna school children, 12 cases were found, a frequency of 0.4 per cent.

Snyder and Curtis (1934) described a family in which 8 cases (4♂ 4♀) occurred in three generations. It was dominant except for one skip, the father in this case having an extremely flat chest. The depression was trough-shaped and just to the right of the midline (Fig. 182). They suggested the name ***koilosternia*** or hollow chest and from blood-group tests concluded that it was probably independent of AB but might be linked with MN. Stoddard (1939) described a large pedigree in Idaho with 49 cases (30♂ 19♀) descended in four generations from seven original cases. There were two degrees of the condition, a slight or a deep depression in the midline, but all affected individuals were apparently heterozygous and the inheritance was dominant without a skip. The gene may be an allele of that in Snyder and Curtis' family. The condition is evidently common enough so that it could be much used for linkage studies. Sweet (1944) describes two sisters with funnel chest, one so extreme that the tip of the sternum touched the vertebrae.

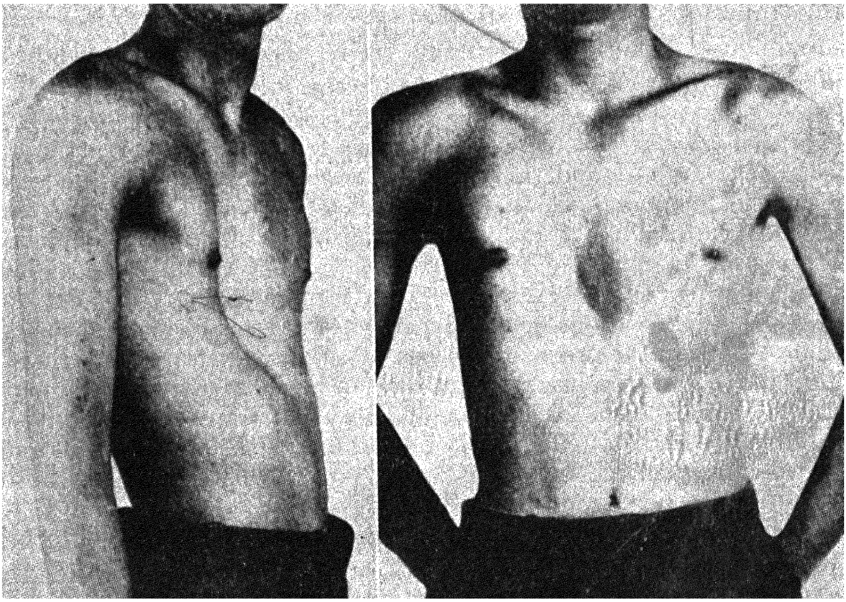

Fig. 182. Two views of funnel chest or koilosternia. (After Snyder and Curtis) (From the *J. of Heredity*)

Three similar cases of *shoulder luxation* in a family are recorded by Valentin (1931). Jordan (1935) records the case of a man with *no sternum*. He was a Syrian, his relatives normal so far as known.

Congenital *subluxation of the acromioclavicular joint* is recorded by Grieve (1944). In medical examination of air crews, six cases, all bilateral, were discovered, and two earlier ones are cited. In one, the father and in another a brother were known to be similarly affected. The condition is probably dominant. The clavicle is raised above the acromion, probably because the conoid and trapezoid ligaments are hypoplastic and elongated. In another case the acromion was deformed on the right side, the right clavicle being hooked. This condition was also present in the father and five of his brothers.

Pelvic Shapes

Sir William Turner (1885) introduced the terms *dolichopellic, mesatipellic* and *platypellic* for the shapes of pelvic inlet. A pelvic index (anteroposterior ÷ transverse diameter) above 95 being dolichopellic, and below 90 platypellic. From measurements of different races (chiefly males) he concluded that Australians, Bushmen, Hottentots, Kaffirs, Andamans and Malays were dolichopellic; Negroes, Tasmanians, New Caledonians and probably Melanesians were mesatipellic; Europeans, Mongolians and Amerindians platypellic. While male Bushmen were dolichopellic, the females were platypellic, and in all races the females were more platypellic than the males. He (1886) made a similar racial classification of sacral indices. Later the conception became general that in European women the transverse oval (platypellic) type was normal. Recent studies by means of X rays show wide variations in the shape of the birth-canal, with the platypellic type by no means the most common.

Recently Caldwell and Moloy (1938), in an X-ray study of the female pelvis in relation to childbirth, recognize (Fig. 183) four types of female pelvis, with a series of intermediates. The dolichopellic (long and narrow) they call *anthropoid*, the flat *platypelloid*, and they recognize two intermediate shapes, *gynecoid* (normal) and *android*, the latter resembling the male pelvis in having a more or less wedge-shaped inlet. They found that the shape of the pelvic inlet could not be accurately determined by the ratio between the conjugate and the widest transverse diameter. A pelvis with platypellic index may be of true flat form or android (wedge-shaped), and variations in the sacrum also affect the pelvic outlet. Thoms (1937) used the four terms *dolichopellic* (anteroposterior exceeding the transverse diameter of the inlet), ***mesatipellic*** (transverse diameter equals or exceeds by no more than 1 cm. the anteroposterior diameter), ***brachypellic*** (transverse diameter exceeding anteroposterior by 1.1–2.9 cm.), ***platypellic*** (transverse diameter exceeding anteroposterior by 3 cm. or more).

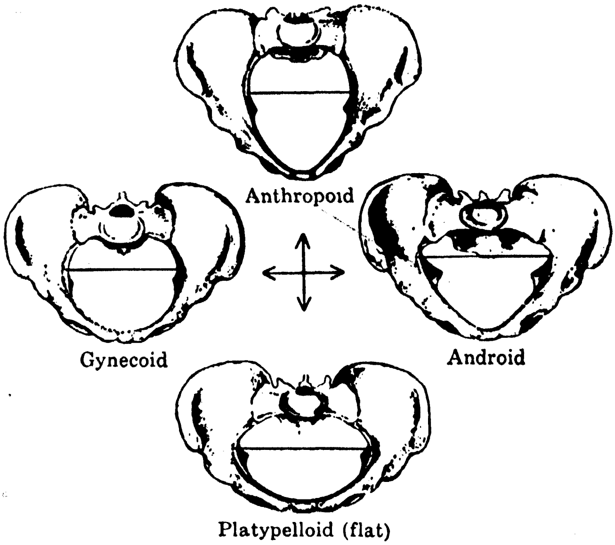

Fig. 183. The four classical types of female pelvis. (After Caldwell and Moloy)

Greulich and Thoms (1939) measured 582 primigravid women in hospital, from X-ray photographs of the pelvis, and compared 100 nurses. They found no constant relation between the type of pelvic inlet and various bodily measurements and proportions. The frequencies of these four types were studied (Caldwell and Moloy, 1939) from the Todd collection of female pelves at Western Reserve University. They found the gynecoid type most frequent, with *ca.* 40 per cent in negro and white women, the platypelloid rare (1–2 per cent) in both. The anthropoid type is more common in Negro women, as Turner pointed out. The android type is more frequent in white women. The platypelloid type is rare, but twice as frequent in white as in Negro women.

Greulich and Thoms (1938a) measured the dimensions of the pelvic inlet from X-ray studies of 789 white females. They found that anteroposterior flattening to produce the dolichopellic type is normal in girls and most common in better nourished women. The platypellic type tended to be produced by unfavorable conditions and it makes for harder childbirth. In a fuller study (1939) they classified 793 white women at the hospital in New Haven, finding 82 per cent of girls, but only 37 per cent of clinic women, dolichopellic, the nurses being 73 per cent of this type.

It is thus clear that the dolichopellic rather than the platypellic type should be regarded as normal. Heyns (1944) recently found the pelvic dimensions of Bantu women less than of English, but similar frequencies of the different types. In a study of six hundred primiparas, Greulich and Thoms found the incidence of operative intervention lowest in dolichopellic and highest in platypellic women. In an anthropometric study of the relation between body build and pelvic shape, it was found that women with long, oval pelves were predominantly tall, dolichocephalic and broad-shouldered with relatively narrow hips. Those with transversely elongated pelves were, on the average, the shortest, with the broadest heads and the narrowest shoulders and the widest pelves in proportion to their shoulders. Women with round pelves were roughly intermediate between the other two types. It is nevertheless impossible to predict pelvic type with certainty from body build, and it was shown that women of the same body build could have any of the three types of pelvis. This is seen in Fig. 184, in which the two women on the right are closely similar in bodily dimensions but extremely different in pelvic type. The two on the left agree in pelvic shape but differ widely in body size. The largest

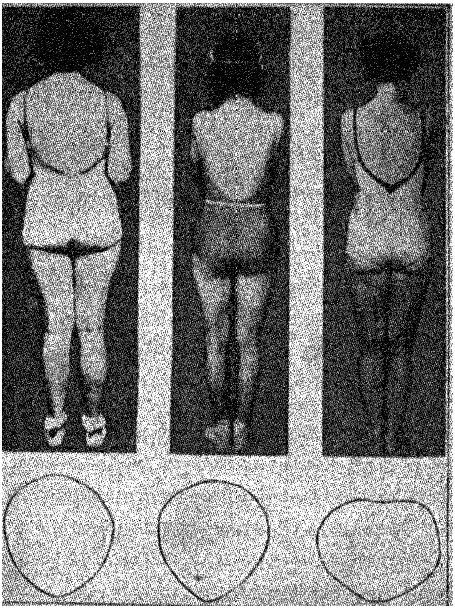

Fig. 184. Relation of pelvic shape to body build. (After Greulich and Thoms)

women in both groups measured had a high incidence of long-oval or round pelves, suggesting that nutritive factors may tend to produce this more favorable type of pelvis. No comparisons have yet been made of mothers and daughters, but Thoms and Greulich (1940) have made a comparative study of male and female pelves. In an X-ray study of 69 white males, Greulich and Thoms (1939a) found the pelvic index to range from 77–121 (mean 100.5), whereas in nineteenth-century textbooks, the mean was 80.8. They found 78.2 per cent dolichopellic, 14.5 per cent mesatipellic, 7.2 per cent platypellic. Sozon-Iaroshevitch (1926) measured the pelves of 321 Russian men. The index ranged from 63–125. They were classed as: 1. Laterally compressed (index 100–125), 43 per cent, this type being found in animals and more frequent in primitive races. 2. Most frequent intermediate type (index 78–100), 68 per cent. 3. Most perfect type (index less than 78), 18.6 per cent, not found in primitive races, most frequent in those of higher culture. The sacral shape was found to correspond with that of the pelvis.

Scheyer (1934) states that the Veddas and the Philippine aborigines have a long, oval pelvic entrance like the orang. He made X-ray photographs of 100 southern Chinese women; 71 were classed as leptosomic and 29 as pycnic, whereas in German women near Cologne the ratio was 50–50. In Canton, 14 Hakka women from the north had mostly a transverse oval pelvis, while Punti women were 55 per cent long oval, 7 per cent round, 38 per cent transverse oval; 46.5 per cent of leptosomic women had long-oval pelves, while 51.7 per cent of pycnic women had transverse-oval pelves. In blood groups, the Hakkas had only 14 per cent O and the Punti 45 per cent O. He thinks that pelvic shape goes with blood group and race.

Thoms (1944) describes four cases of *Naegele pelvis* in women, indicating that the condition is much more common than supposed. It was recognized by Naegele in 1803 and fully described by him in 1839. This particular type of asymmetrical pelvis, clearly shown by X-ray photographs, is evidently germinally determined in most cases and it may prevent natural childbirth. Of Thoms' four cases, one is an Irish woman, two Italian and one American. There may be a corresponding male condition. Further study should determine the manner of inheritance.

Tails

The phylogenetic loss of a tail in the Primates and man is a matter of great evolutionary interest. Indications as to how it happened can perhaps be obtained from the genetics of the many tailless and short-tailed mutations in other mammals. More or less completely tailless mutations have occurred in dogs, cats, rats, mice, sheep, goats, cattle, horses and pigs. Rumplessness in fowls, which has been much studied, is the corresponding condition in birds. It occurs as a mutation in certain breeds of fowls and Landauer (1945) has recently shown that it can also be produced by injection of insulin and certain other chemicals into the egg. In one experiment with Leghorn eggs, 42 per cent of the embryos surviving to the seventeenth day were rumpless. There was no significant rise in other abnormalities. Loss of a tail is not, however, confined to domestic animals, but is a specific character in the guinea pig, as it is in man. Some species of rabbits have a very short tail, as do some species of deer. All our domestic animals have produced tailless variations, whereas taillessness has become a specific character only in certain scattered wild species and groups. There is no obvious reason why a guinea pig should have less need of a tail than a cat. The tailless mutation is by no means uncommon in cats, as we shall see, yet the natural species retains its tail while its near relative, the lynx, which also climbs trees and has similar habits, retains only a stub. In these circumstances, something more than an assumed selection of mutations is necessary to account for the loss of a tail in some species and its retention in others. Similarly, while most of the monkeys and baboons have retained long tails, frequently prehensile in New World monkeys, the Barbary ape has only a very short stump of a tail, probably the caudal filament. Schultz (1925) records, on the other hand, that in the adult chimpanzee and orang, which are normally tailless, the caudal filament has been known to persist. It is recognized that in the orang the loss of a tail has proceeded farther than in man, since he has only two or three rudimentary coccygeal vertebrae whereas man has four to five or sometimes six. The caudal region is also more vestigial in the gibbon than in man.

The relatively recent loss of a tail in man is indicated by the reappearance of an atavistic tail as a rare event. The anomaly is less rare than might be supposed. Bartels (1884) wrote an extensive monograph full of interesting lore on the subject of human tails. Pliny and Pausanius refer to tailed human beings and there was formerly widespread belief in the existence of human races with a tail. The traditional devil[1] may be regarded as a survival from these legends. The human embryo has a caudal appendage which, at one stage of the baby's development, is one-sixth its total length; if absorption fails to take place, the infant may be born with it attached. The human embryo at the seventh week, when *ca.* 12 mm. long, has eight to ten caudal segments. A well-developed tail is still represented in the human germplasm, but a time factor is involved in the cessation of its growth and then the activity of other genes in development causes it to be completely absorbed long before birth. The tide of development, which at first flows into it, afterwards flows away and leaves it as a remnant to be mopped up by the developing organism.

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[1] Seals bearing this tailed human figure were found at Mohenjo-daro, the earliest known civilization of India, perhaps 4000 B.C.

Stockard (1930) has emphasized essentially the same view in relation to the reappearance of long-lost toes in guinea pigs and dogs. The dog lost one digit in its evolution, which reappears in certain breeds as a simple dominant character; jostling of the genes has determined its reappearance. Bartels recorded 126 cases of human tails (52♂ 16♀, 58 sex unknown), including in his list some abnormalities of other kinds.

Schaeffer (1892) added twenty-five more cases, but these were a very heterogeneous collection of anomalies. In the collected works of Robert Koch, Vol. ii, p. 822, are two photographs of human beings with tails "as long as a human foot." The photographs were taken in India in 1871, one a lad of seventeen, the other a child, but apparently these tails contained no bones. Lissner (1885) records the very rare case of a girl born to normal parents, with a true cauda perfecta 12.5 cm. long, a continuation of the vertebral column, but with a cyst attached. The child was well nourished and had several normal sibs. The parents refused to have the baby's tail removed, and at thirteen and a half years of age she ceased going to school, (*a*) because of pain from sitting on the tail, and (*b*) because she was teased by the other scholars. There is no evidence that in these cases there are any additional vertebrae besides those of the coccyx. Sernoff (1902) regarded all such cases as atavisms, probably associated with a tendency to spina bifida.

Harrison (1901) reviewed the subject and gives many references besides describing a boy with a soft tail 4.4 cm. long at birth, which grew to a length of 7 cm. before it was removed at the age of six months. It bore some resemblance to a pig's tail and could be partly retracted. Harrison described its histology and noted that the baby was the third in the family, a normal, healthy baby, except that the four outer toes of the right foot were shorter than the normal ones of the left foot, their tips were turned up and the nails were small and thick. These four toes had only two short phalanges, so this was a case of partial brachydactyly. A similar tail (Keith in *Nature* 106: 845. 1921) was removed from a girl at three months. It was 10.5 cm. long and 11 mm. in diameter at the base.

Schultz (1925) figures a twelve-year-old boy from French Indo-China with a tail 9 in. long. The five-weeks embryo has a tail and 38 vertebrae instead of 33 or 34. At six weeks the last three vertebrae are fused and at nine weeks the number is 34. Eliseef (no ref.) described a girl with a tail 36–45 mm. long, covered with hair. It grew longer at puberty and prevented her sitting in comfort. Her mother's mother also had a tail.

Schwarz (1912) gives two photographs of a well-developed male infant with a soft tail 5½ cm. long and no other malformations (Fig. 185). It was 1 cm. in diameter at the thickest part, with a constriction at the base. He recognized five classes of human tails. There are only three recorded cases of a tail with vertebrae.

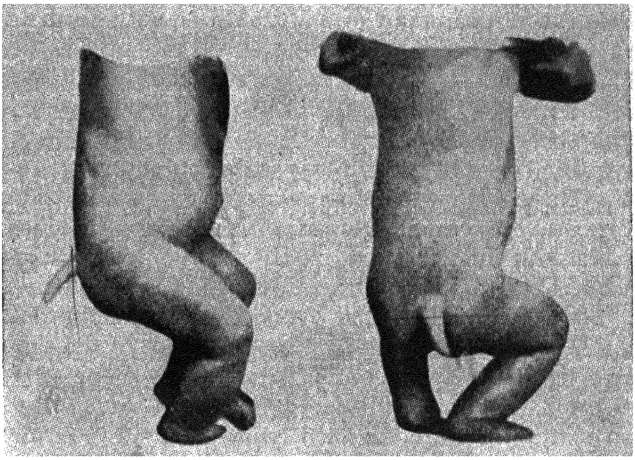

Fig. 185. Child with a tail 5½ cm. long. (After Schwarz)

A comparison of the vertebral columns of man, anthropoid apes and monkeys has been made by Fischer (1933), who shows in a table the comparative lengths of the thoracic, lumbar, sacral and caudal portions. He assumes that anthropoids did not lose their tails through natural selection. There is the same shifting of the boundaries between the different types of vertebrae in the gorilla, chimpanzee and man. It would seem that the loss of tail in man and the anthropoids must have happened through a series of loss mutations, which may even have taken place independently in different genera.

The numerous studies of loss of tail and kinky tail in various mammals can only be summarized here. It is clear that tailless or short-tailed mutations are relatively common and have occurred repeatedly. Bamber (1927) surveyed the literature regarding tailless cats. The Manx (or rumpy) cat has several caudal vertebrae under the skin. In crosses with long-tailed cats the F_1 has every length of tail from none to full length. This is like the F_1 in a cross (Gates, 1909) between the tailless Old English Sheep dog and the Scotch collie. Vilmorin (1913) used three tailless and three short-tailed breeds of dogs in crosses with long tail. He obtained 52 per cent with a long tail and 48 per cent with a short tail or none. In crosses between short-tailed parents he obtained 7 with long tail : 14 with a short tail or none, He concluded that short tail is a dominant mutation, the homozygous condition being lethal.

Tailless cats are also known in the Crimea, cats with twisted tails in Madagascar, a kinked tail in some Siamese and Malay cats and short tails in Japanese cats. Other tailless cats are known from Pegu, Malacca, Burma, China, Borneo, England, France and Spain. Kennel (1901) described a tailless cat mutation in Germany. Mated with normals it produced six litters, 12 long : 4 stumpy : 12 tailless. If the tailless mutation was dominant (**T**), then **Tt** × **tt** would give 1 : 1. Stumpy tails probably indicate incomplete dominance due to the presence of modifiers.

Screw-tail has been described in cattle, as well as kinky tail in pigs and mice. Kinky tail in pigs (Nordby, 1934) is due to unilateral fusion of adjacent caudal vertebrae. If two vertebrae are fused on both sides no kink is produced. A recessive factor is involved; but kinks appear in less than 1 : 3, partly from bilateral fusions and partly from "inhibitory influences." Huestis and Barto (1936) found the same condition in the deer-mouse, Peromyscus. They obtained normal overlaps and thought that two recessive genes were involved. Wrytail, in which the base of the tail is set to the left, appears to be a widely disseminated recessive gene in Jersey cattle (*J. Hered.* 26:331). Atkeson, Eldridge and Ibsen (1944) show that it is a simple recessive in Jerseys and Brown Swiss cattle. It is also known in Guernsey, Holstein and Ayrshire cattle. Koch (1935) points out that in breeds of dogs with a short head, such as the bulldog, a cork-screw tail frequently appears, and ascribes the condition to lack of antepituitary growth hormone.

Brachyury is a dominant in the mouse, lethal in the homozygous condition (Dobrovolskaia-Zavadskaia, 1927). The homozygotes die *in utero* at *ca.* eleven days. Chesley (1935) showed that embryos homozygous for short tail are indistinguishable from normals up to the pre-somite stage. In later stages the somites and neural tube are irregular, the notochord absent and the region of the posterior limbs entirely missing. Dorsal blebs were found in early stages. This is a good example of a gene which produces little effect in the heterozygous state but produces fundamental derangements, with lethal effect, in the homozygous condition.

In crossing this strain with wild mice, three strains have arisen with complete absence of bony tail (anury). They breed true for taillessness, apparently due to balanced lethals (Dunn, 1939). Chesley and Dunn (1936) showed that two factors, **T** and $\mathbf{t}^0$ were present, probably alleles and each a homozygous lethal. Dunn *et al.* (1939) recognized that there are several brachyuric and anuric mutations at or near one genetic locus. While **T** is lethal to the embryo in eleven days, from a deficiency in notochord development, $\mathbf{t}^1\mathbf{t}^1$ is lethal before implantation. $\mathbf{t}^0\mathbf{t}^0$ can be recognized *in utero* at *ca.* five days (Gluecksohn-Schoenheimer, 1940). Development then stops and resorption takes place. It is probably a third allele. From the embryology of $\mathbf{Tt}^0$ hybrids it was concluded that $\mathbf{t}^0$ affects the development of the mesoderm.

At least six different mutations and probably several more affecting the tail are now known in the house mouse. In addition to the three already mentioned, the flexed-tail mutation affects the intervertebral cartilages and produces an embryonic and juvenile anaemia (Dunn *et al.*, 1940). It was shown by Kamenoff (1935) that this recessive gene produces fusion between neighboring vertebrae, both in the tail and in the spinal column. There is a lower rate of cell division in the embryogeny of the intervertebral discs. The accompanying anaemia begins as early as fourteen days after fertilization. The relation between these two effects of the gene is not clear. "Shaker short" modifies the development of the end of the tail and alters the growth of the brain and the internal ear, affecting the behavior. "Fused" and "kink" are other tail mutations which produce profound and widespread effects. These authors also describe a mutation, **Sd,** which produces in the heterozygous condition a short tail or none, a short or crooked spine, with abnormal kidneys and low viability. The homozygotes have (1) no tail, (2) spina bifida, (3) absence of kidneys, external genitalia and other parts of the urinogenital system. They die at birth. This condition segregates as a unit and the heterozygotes have such low viability that the condition is virtually a dominant lethal. A further study of this condition was made by Gluecksohn-Schoenheimer (1940). Anatomically similar conditions have been described in man.

Caspari and David (1940) describe a kinky tail mutation in mice, which is like fused, but it also shows waltzing and deafness. It is a simple dominant, the homozygote being almost completely lethal.

Genetic conditions regarding the tail of the rat appear to be quite different from those in mice. Dunn *et al.* (1942) find that nineteen cases of sporadic taillessness in the rat have been recorded. Of these, sixteen were found by King (1931) among 171,000 white rats in the period 1907–1930, i.e., with a frequency of 1 in 10,000. This is somatic "amputation." None of their descendants were tailless, even when two tailless rats were bred together. Similarly, Hutt and Mydland (1932) found no tailless rats among 229 descendants of such a case. These are not mutations but sporadic "accidents." Dunn and his collaborators have, however, found three inbred families of rats from different sources, which produced tailless individuals with a frequency of 1.3 per cent, 1.6 per cent and 3.7 per cent (39 in 1166) respectively. These are not mutation frequencies in the ordinary sense, for the tailless condition is not inherited. The tails were resorbed in embryonic development and in one family all thirteen tailless mice were females. A recessive gene is not involved, but animals with or without a tail have the same genetic constitution. Something in the genotype determines how much "environmental pressure" need be applied to produce the tailless condition through accidental irregularity in the environment of the embryo. This rather new principle is important in connection with some human abnormalities. It means that one cannot always assume with certainty that any new abnormality is really a mutation. *What is inherited is a tendency to produce a particular abnormal non-inherited condition with a certain frequency.* This situation probably applies to many conditions in man, and needs to be carefully distinguished from the ordinary type of recessive or dominant mutation.

Another gene in mice, resembling flexed tail, was discovered by Crew and Auerbach (1941) and named *pigtail*. It shows various degrees of expressivity and incomplete penetrance. There are no abnormal bones, and spina bifida aperta occurred in some of the highly inbred litters. This recessive twisted-tail condition is caused either by two complementary factors or by one main gene with modifiers which affect penetrance (i.e., inhibitors). The penetrance varies around 20 per cent. There is slight negative correlation between litter-size and the percentage of manifestation in homozygous litters, suggesting some intra-uterine non-genetic influence on the development of the abnormality.

Stub tail has appeared in rats as a simple recessive mutation (Ratcliffe and King, 1941). It appeared in the eighth generation of a strain of cinnamon rats derived by mutation from wild gray Norway rats which had been bred in captivity for many generations. This gene appears to be homologous with the **Sd** gene in mice. In homozygous animals the tail is deformed as well as short and the great majority die at birth, so the condition is sublethal. Homozygotes also have frequent malformations in the posterior region of the body, with small size accompanying the reduced viability. Some of the non-viables had only a shortened tail, others lacked the anal and urinary openings. In a few the hind legs were fused. Deformed lateral toes were frequent on the fore and hind feet, as well as aplasia of one kidney and atresia of the ureters. Histological evidence of hyperthyroidism was found regularly in males and in about half of the females. Only three affected females bred. The condition shows much variation in expressivity.

In an earlier record (Conrow, 1917) eleven tailless rats were observed among some 71,500 bred at the Wistar Institute. The vertebral column ended far in front of the posterior end of the body. One lacked all four sacral and one or two lumbar vertebrae. These congenitally tailless rats were bred, but in the absence of records of inheritance they may have been non-heritable "somatic accidents" like the mice already recorded.

In cattle, Mohr and Wriedt (1930) described a recessive lethal in a mountain breed of Norway. In the homozygote, which dies at birth, there is extreme shortening of the spinal column, with fusion of many vertebrae and ribs. The neck is very short and the insertion of the stub tail is very high, the animal having an elk-like appearance with normal head and legs. Wriedt and Mohr (1928) described another recessive lethal in which the skeletal changes were practically the reciprocal of the last, i.e., the spinal column, ribs and sternum were normal while the maxillary, mandibular and hyoid regions of the skull were reduced, there was cleft palate, the forelegs were "amputated" at the elbow joint and the hind legs at the hock.

MacDowell *et al.* (1942) have described a screwtail mutation in the albino mouse, which is remarkable for its pleiotropic effects. It is a simple recessive, with a 2 per cent deficiency in early litters from heterozygous parents, the screw tails being largely eliminated by intrauterine selection in later litters. In addition to the twisted tail, there are effects on (2) pelvis, (3) vertebrae, (4) sternum, (5) mandibles, (6) molar and incisor teeth, (7) external ears, (8) eyelids exuding a sticky substance, (9) cranial sutures, (10) feeding habits, (11) size, (12) mortality, (13) fertility.

The tail mutations in mammals are collected in Table 15, mainly from Steiniger (1938). Bryson (1944) has recently shown that t^0 and t' both affect spermatogenesis in the mouse, the two together producing complete sterility.

TABLE 15

TAIL MUTATIONS IN MAMMALS

Species	*Description*	*Symbol*	*Inheritance*	*Lethal Effect*	*Observed Orig.*
Dog	short tail	**T**	dominant	homozy. lethal	Once (doubtful)
Dog	screw tail	**f (?)**	recessive		——
Fox	short tail	**T**	dominant (?)	?	——
Cat	tailless	**T**	dominant	homozy. lethal	——
Mouse	tailless & short tail	**T**	dominant	homozy. lethal	4*
Mouse	modifier for t	**t^0**	dominant	homozy. lethal	——
Mouse	modifier for t	**t'**	dominant	homozy. lethal	——
Mouse	kinky tail	**f(k)**	recessive	homozy. lethal	——
Mouse	fused	**Tf**	dominant	——	——
Mouse	D-short	**Sd**	dominant	——	——
Mouse	shaker-short	**s^t**	recessive	homozy. sublethal	——
Mouse	hydrocephalus with kinky tail	**hyd I**	recessive	homozy. sublethal	——
Peromyscus	kinky tail	——	rec. prob. dimeric	——	——
Cattle	screw tail	**f (?)**	recessive	——	——
Cattle	short tail	**T (?)**	dominant (?)	——	——
Sheep	tailless	——	dominant (?)	?	——
Swine	kinky tail	**f (?)**	recessive	——	——

* This mutation was observed four times under controlled conditions.

It is evident that many different genes have been involved in the shortening, twisting or loss of a tail in mammals. The phylogenetic reduction of tails in the Primates must have happened by a series of such genetic steps. Tail reduction involves changes in embryological development, which can be produced by different genes. It depends on special capacities of the caudal region for mutational changes. This could be explained on the basis of a progressive embryonic gradient from the cranial to the caudal region. Shortening and loss of tail appears to be another example, on a large scale, of *parallel mutations producing phyletic effects in different groups of mammals.* But the evolutionary reason why this mutational loss of a tail took place in all the Primates remains obscure.

Fisher and Holt (1944) find that by crossing **Sd** mice with normal, followed by selection, the tail-length of the segregates can be gradually increased to five-sixths of the normal length. Dunn and Landauer (1934) found that rumplessness, the corresponding condition in fowls, could be changed from dominant to recessive by crossing of intermediates with normal.

Dunn and Gluecksohn-Schoenheimer (1944) describe an abnormal condition in tailless mice, in which both anal and genital openings are lacking and the young die shortly after birth. The posterior parts of the gut and urinary duct fail to develop and often remain connected to form a cloaca without opening. This syndrome is found in mice having eleven different genes or gene combinations, all affecting the tail, but does not appear when only **T**, $\mathbf{t}^0$ or **t′** are present — only when the animals have two or more of the following mutations: **Sd**, a dominant producing short tail and kidney defects in the heterozygote, the full syndrome together with spina bifida aperta in homozygotes; **Ki** (kinky tail); **Fu**, a semilethal closely resembling **Ki**. Gluecksohn-Schoenheimer (1945) in a fuller study of the **Sd** gene, in which the homozygotes are grossly defective and lethal, finds that the first abnormality in heterozygotes appears in the tail in development ten days after fertilization. Small hematomata and products of cell degeneration occur and this part of the tail is resorbed. Abnormalities of the notochord and of the neural tube are secondary to the tail degeneration. Metanephric abnormalities are dependent on those of the ureters. In homozygotes the metanephric duct is absent, the ureters short, displaced and frequently doubled. By tracing such abnormalities to their source in development, much may be learned of their ultimate genic nature.

Pryor (1907) studied the *order of ossification of the eight carpal bones* in ten families of children, based on 360 skiagraphs of children generally under seven years of age. The order was symmetrical in both hands but varied in different families. He concluded that differences in order of ossification were inherited. In a later study (1939), he applied the method to multiple births. He confirmed that the Kerner triplets were MZ by showing the same order of ossification of the carpal bones. In the Schense quadruplets the ossification order tends to confirm that they are 2 + 1 + 1, i.e., derived from three egg cells. In the Morlok quadruplets, all eight hands show the same sequence and there is an extra epiphysis at the end of the second metacarpal in all eight hands. The conclusion is clear that variations in the sequence of carpal ossification are genetically determined. Pryor (1936) found that six years and one month was the best age for determining the order of carpal ossification. The gene complex determines the entire pattern in which the carpal bones are laid down, first in cartilage and then in bone. X rays of these bones in the Perricone male quadruplets confirms that they are a four-egg set although all of the same sex. This condition must be extremely rare. In A there were four centres of ossification in each hand and the metacarpals and phalanges were much shorter than in the other three. B at the same age had four ossification centres in the right hand and five in the left and they were in a different sequence. C had only three centres in each carpus, and D had six in the right and seven in the left.

LITERATURE

Albers-Schönberg, H. E. 1915. Eine seltene, bisher nicht bekannte Strukturanomalie des Skelettes. *Fortschr. Roentgenstr.* 23:174–175. Figs. 4.

Aschner, B. 1928. Zur Erbbiologie des Skelettsystems. *Zeits. f. Konstlehre* 14:129–211.

Atkeson, F. W., Eldridge, F. & Ibsen, H. L. 1944. Prevalence of "wrytail" in cattle. *J. Hered.* 35:11–14. Figs. 2.

Baldwin, W. M. 1915. The artificial production of spina bifida. *Anat. Rec.* 9:365–381. Figs. 16.

Bamber, R. C. 1927. Genetics of domestic cats. *Bibl. Genet.* 3:1–86.

Barraquer, L. & de Gispert, I. 1936. La siringomielia enfermedad familiar y hereditaria (13 casos en dos generaciones de una misma familia). *Clin. y lab.* 29:322–329.

Bartels, M. 1884. Die geschwänzten Menschen. *Arch. f. Anthrop.* 15:45–131. Pls. 2.

Baumgartner, I. N. 1945. The inheritance of developmental patterns of rib ossification in the rabbit. *Genetics* 30:1 (Abst.).

van Bogaert, L. 1933. Über eine hereditäre und familiäre Form der Paget-schen Ostitis deformans mit Chorioretinitis pigmentosa. *Zeits. f. ges. Neurol.* 147:327–345. Figs. 7.

———. 1934. Syringomyelie bei zwei Schwestern, in einem der Fälle Vorhandensein einer Kleinhirncyste. Anatomischklinischer Beitrag. *Ztschr. f. ges. Neurol. u. Psychiat.* 149:661–677.

Bonnevie, K. 1936. Pseudencephalie als spontane recessive (?) Mutation bei der Hausmaus. *Skrifter Norsk. Vid.-Akad.* 2: No. 9, pp. 39. Pls. 7.

Braun, K. 1939. Eine Beobachtung von konkordanten Wirbelsäulenverbiegungen und Fussdeformitäten mit gleichzeitiger diskordanter Hüftluxation bei einem einiigen Zwillingspaar. *Der Erbarzt* 6:48–49. Figs. 2.

Brücke, H. 1933. Über multiple Enostosen (Osteopoikilie). *Deut. Zeit. f. Chir.* 239:554–564. Figs. 5.

Bryson, V. 1944. Spermatogenesis and fertility in *Mus musculus* as affected by factors at the T locus. *J. Morph.* 74:131–186. Pls. 4.

Caffey, J. & Silverman, W. A. 1945. Infantile cortical hyperostoses. *Am. J. Roentgenol.* 54:1–16. Figs. 17.

Caldwell, W. E. & Moloy, H. C. 1938. Anatomical variations in the female pelvis: their classification and obstetrical significance. *Proc. Roy. Soc. Med.* 32:1–30. Figs. 15.

———. 1939. Anatomical variations in the female pelvis. *Edinb. Med. J.* 46: Suppt. 1–48. Figs. 16.

Camp, J. D. 1926. The sella turcica. *J. Am. Med. Assn.* 86:164–168. Figs. 10.

Camp, J. D. & Nash, L. A. 1944. Developmental thinness of the parietal bones. *Radiology* 42:42–47. Figs. 5.

*Camurati. 1922. *La Chirurgia degli Organi di Movimento.* Bologna.

Carr, J. G. 1933. The cardiac complications of Trichterbrust. *Ann. Int. Med.* 6:885–894. Figs. 3.

Caspari, E. & David, P. R. 1940. The inheritance of a tail abnormality in the house mouse. *J. Hered.* 31:427–431. Figs. 2.

Caussade, L., Niemann, N. & Mariot. 1937. Pertes de substances familiales, héréditaires et congenitale de la voûte cranienne. *Presse Med.* 45:1124.

Chesley, P. 1935. Development of the short-tailed mutant in the house mouse. *J. Exp. Zool.* 70:429–459. Pls. 2.

Chesley, P. & Dunn, L. C. 1936. The inheritance of taillessness (anury) in the house mouse. *Genetics* 21:525–536.

Claussen, F. 1939. Phänogenetik vom Menschen. *Zeits. f. Abst. u. Vererb.* 76:14–46. Figs. 16.

Conrow, S. B. 1917. Further observations on taillessness in the rat. *Anat. Rec.* 12:155–159. Figs. 3.

Crew, F. A. E. & Auerbach, C. 1941. "Pigtail," a hereditary tail abnormality in the house mouse. *J. Genet.* 41:267–274. Pls. 2, figs. 2.

Crooks, J. 1932. Two unusual examples of osteogenesis imperfecta. *Brit. Med. J.* i. 705.

Dahlberg, G. & Diamant, M. 1945. Inheritance of pneumatization of the mastoid bone. *Hereditas* 31:441–456.

Dalquest, W. W. & Scheffer, V. B. 1944. Distribution and variation in pocket gophers, *Thomomys talpoides*, in the State of Washington. *Amer. Nat.* 78:308–333. Figs. 4.

Deniker, J. 1913. *The Races of Man.* London, New York. Pp. 611.

Dickson, D. D., Camp, J. D. & Ghormley, R. K. 1945. Osteitis deformans. *Radiology* 44:449–470. Figs. 4.

Dillon, J. G. & Gourevitch, J. B. 1934. A twin study of pneumatization of the nasal accessory sinuses, mastoid processes and the form and dimensions of the sella turcica. *Trudy Med.-Genet. Inst. Gorky* 3:68–72. Figs. 2. (Russian with English summary.)

Dobrovolskaia-Zavadskaia, N. 1927. Sur la mortification spontanée de la queue chez la souris nouveau-née et sur l'existence d'un caractère (facteur héréditaire) non-viable. *C. R. Soc. de Biol. Paris* 97:114–119.

Dunn, L. C. 1939. Taillessness in the balanced lethal line 19. *Genetics* 24:728–731.

Dunn, L. C. & Gluecksohn-Schoenheimer, S. 1939. Taillessness in a second (balanced) lethal line. *Genetics* 24:587–609.

———. 1944. A specific abnormality associated with a variety of genotypes. *Proc. Nat. Acad. Sci.* 30:173–176.

Dunn, L. C., Gluecksohn-Schoenheimer, S. & Bryson, V. 1940. A new mutation in the mouse affecting spinal column and urinogenital system. *J. Hered.* 31:343–348. Figs. 4.

Dunn, L. C., Gluecksohn-Schoenheimer, S., Curtis, M. R. & Dunning, W. F. 1942. Heredity and accident as factors in the production of taillessness in the rat. *J. Hered.* 33:65–67. Fig. 1.

Dunn, L. C. & Landauer, W. 1934. The genetics of the rumpless fowl, with evidence of a case of changing dominance. *J. Genet.* 29:217–243. Fig. 1.

DuToit, F. 1931. A case of congenital elevation of the scapula (Sprengel's deformity) with defect of the cervical spine associated with syringomyelia. *Brain* 54:421–429. Figs. 3.

Ebstein, W. von. 1882. Über die Trichterbrust. *Deut. Arch. f. Klin. Med.* 30:411–428.

Edeiken, J. & Wolferth, C. C. 1932. The heart in funnel chest. *Am. J. Med. Sci.* 184:445–452. Figs. 4.

Ellis, R. W. B. 1938. Congenital parietal foramina. *Proc. Roy. Soc. Med.* 31:923.

Enderle, C. 1933. Beitrag zur Kenntnis der familiären myelodysplasischen Syndrome und des "Status dysraphicus." *Zeits. f. ges. Neurol.* 146:747–766. Figs. 6.

Fell, H. B. & Grüneberg, H. 1939. The histology and self-differentiating capacity of the abnormal cartilage in a new lethal mutation in the rat. *Proc. Roy. Soc. B.* 127:257–277. Pls. 3.

Field, C. E. 1938. Albers-Schönberg disease; an atypical case. *Proc. Roy. Soc. Med.* 32:320–324. Figs. 5.

Fischer, E. 1933. Genetik und Stammesgeschichte der menschlichen Wirbelsäule. *Biol. Zentbl.* 53:203–220.

Fisher, R. A. & Holt, S. B. 1944. The experimental modification in Danforth's short-tailed mutant mice. *Ann. of Eugen.* 12:102–120.

Ford, J. A., Quimby, G. I., Jr. & Snow, C. E. 1945. The Tchefuncte culture, an early occupation of the Lower Mississippi Valley. *Am. Antiquity Suppt.* 10: No. 3. Pp. 113, pls. 12, figs. 23.

Fouché, L. 1937. *Mapungubwe, ancient Bantu civilization on the Limpopo.* Cambridge Univ. Press. Pp. 184.

Frary, Louise G. 1935. Enuresis: a genetic study. *Am. J. Dis. Child.* 49:557–578.

Frede, M. 1934. Untersuchungen an der Wirbelsäule und den Extremitäten-plexus der Ratte. *Zeits. f. Morph. u. Anthrop.* 33:96–150. Pls. 4.

Frey, H. 1924. Weitere Untersuchungen über die Scapula, speziell über die Scapula scaphoides. *Zeits. Anat. Entw-gesch.* 74:240–284. Figs. 12.

Garland, H. G. 1934. Hereditary scoliasis. *Brit. Med. J.* i. 328.

Gates, R. R. 1909. A litter of hybrid dogs. *Science* 29:744–747.

Gluecksohn-Schoenheimer, S. 1940. The effect of an early lethal (t^0) in the house mouse. *Genetics* 25:391–400. Pl. 1, Figs. 6.

Gluecksohn-Schoenheimer, S. 1941. On a new short-tail mutation. *Proc. Genet. Congr. Edinb.* P. 255.

———. 1945. The embryonic development of mutants of the Sd-strain in mice. *Genetics* 30:29–38. Pl. 1.

Godlee, R. J. 1909. The torus palatinus. *Proc. Roy. Soc. Med.* 2: Part 3, (Surg.) 175–176.

Goldsmith, W. M. 1922. The Catlin mark: the inheritance of an unusual opening in the parietal bones. *J. Hered.* 13:69–71. Figs. 5.

———. 1941. Bilateral fenestrae in the parietal bones. *J. Hered.* 32:301–309. Figs. 7.

Goodman, A. L. 1915. Congenital depressions of the skull. *Arch. of Pediat. N. Y.* 32:587–589. Figs. 3.

Gottesleben, A. 1927. Über den doppelseitigen und einseitigen Schulterblatthochstand. *Arch. Klin. Chir.* 144:723–731. Figs. 9.

Graves, W. W. 1910. The scaphoid scapula. *Med. Record* May 21. Figs. 8.

———. 1921. The types of scapula. *Am. J. Phys. Anthrop.* 4:111–128. Pls. 5.

———. 1922. Observations on age changes in the scapula. *Am. J. Phys. Anthrop.* 5:21–33. Pls. 5.

———. 1924. The relations of scapular types to problems of human heredity, longevity, morbidity and adaptability in general. *Arch. Int. Med.* 34:1–26. Figs. 5.

———. 1931. Scapular types and human fitness. *Eugen. Review* 23:215–221. Figs. 2.

———. 1932. A note on inherited variations and fitness problems. *Decade of Progr. in Eugenics,* 457–480.

Green, E. L. 1941. Genetic and non-genetic factors which influence the type of the skeleton in an inbred strain of mice. *Genetics* 26:192–222. Fig. 1.

Green, E. L. 1939. The inheritance of a rib variation in the rabbit. *Anat. Rec.* 74:47–60.

Greulich, W. W. & Thoms, H. 1938. Body build and pelvic type in white women. *Am. J. Phys. Anthrop.* 23:502. (Abst.)

——— ———. 1938a. Dimensions of pelvic inlet in 789 white females. *Anat. Rec.* 72:45–51.

——— ———. 1939. A study of the pelvic type and its relationship to body build in white women. *J. Am. Med. Assn.* 112:485–493. Figs. 10.

——— ———. 1939a. An X-ray study of male pelves. *Anat. Rec.* 75:289–299. Pls. 3.

Grieg, D. M. 1892. On congenital and symmetrical perforation of both parietal bones. *J. Anat. & Physiol.* 26:187–191.

———. 1917. Congenital and symmetrical perforation of both parietal bones. *Edinb. Med. J.* 18:205–209.

———. 1924. Congenital high scapula. *Edinb. Med. J.* 31:22–44. Figs. 24.

———. 1926. On symmetrical thinness of the parietal bones. *Edinb. Med. J.* 33:645–671.

———. 1927. Abnormally large foramina parietalia. *Edinb. Med. J.* 34:639–648. Figs. 12.

Grieve, J. 1944. Congenital subluxation of acromioclavicular joint. *Lancet* 247:817–818.

Grüneberg, H. 1938. An analysis of the "pleiotropic" effects of a new lethal mutation in the rat (*Mus norvegicus*). *Proc. Roy. Soc. B.* 125:123–144. Pls. 3.

Halbertsma, T. G. 1940. Fenestrae parietales symmetricae. *Arch. of Dis. Child.* 15:115–120. Figs. 7.

Hanhart, E. 1942. Über sublethale Mutationen beim Menschen. *Arch. J. Klaus. Stift.* 17:485–489.

———. 1943. Ergebnisse der Erbforschung von Erbkrankheiten und Missbildungen in der Schweiz. *Arch. J. Klaus-Stift.* 18:632–661.

Harrison, Ross G. 1901. On the occurrence of tails in man, with a description of the case reported by Dr. Watson. *Johns Hopkins Hosp. Bull.* 12:96–101. Figs. 6.

Hauck, H. 1942. *Zeits. mensch. Vererb. Konst-lehre* 26:376–385.

Hertwig, O. 1896. Experimentelle Erzeugung thierischer Missbildungen. *Festschr. f. Gegenbaur* 2:87–101. Pl. 1.

Herzenberg, H. & Levit, S. G. 1931. Über die Genetik der Marmorkrankheit. *Zeits. Abst. Vererb.* 59:349–364. Figs. 9.

Heston, W. E. 1938. Bent-nose in the Norway rat. *J. Hered.* 29:437–448. Figs. 2.

Heyns, O. S. 1944. A study of the Bantu female pelvis. *J. Anat.* 78:151–167. Fig. 1.

Hobbs, A. A., Jr. 1944. Hereditary factors in multiple congenital deformities. *Am. J. Roentgenol.* 51:677–681. Figs. 4.

Hooton, E. A. 1930. *The Indians of Pecos Pueblo.* Yale University Press, Pp. 391, pls. 97.

Hrdlička, A. 1942a. The scapula: visual observations. *Am. J. Phys. Anthrop.* 29:73–94. Figs. 5.

———. 1942b. The juvenile scapula: further observations. *Am. J. Phys. Anthrop.* 29:287–310. Fig. 1.

———. 1942c. The adult scapula: additional observations and measurements. *Am. J. Phys. Anthrop.* 29:363–415. Figs. 6.

Huestis, R. R. & Barto, E. 1936. Flexed-tailed Peromyscus. *J. Hered.* 27:73–75. Figs. 2.

Hutt, F. B. & Mydland, O. 1932. Congenital taillessness in the rat. *J. Hered.* 23:363–367. Figs. 2.

Jaffe, H. L., Bodansky, A. & Blair, J. E. 1930. Erzeugung von Ostitis fibrosa (Osteodystrophia fibrosa) durch Epithelkörperchen-Extrakt. *Klin. Wochens.* 9:1717–1719.

Jensch, N. 1942. Zur Genealogie und Klinik des Turmschädels. *Arch. f. Psychiat.* 114:444–505. Figs. 8.

Jordan, A. 1935. A case of congenital defect of the sternum. *Lancet* 229:877.

Kamenoff, R. J. 1935. Effects of the flexed-tail gene on the development of the house mouse. *J. Morph.* 58:117–152. Pls. 2.

Karshner, R. G. 1926. Osteopetrosis. *Am. J. Roentgenol.* 16:405–419. Figs. 6.

Kay, H. D., Simpson, S. L. & Riddoch, G. 1934. Osteitis deformans. *Arch. Int. Med.* 53:208–248. Figs. 5.

Keeler, C. E. 1933. Interfrontal — A heritable cranial variation in the house mouse. *J. Mammal.* 14:75–76. Fig. 1.

———. 1941. Hereditary shape differences in the foramen magnum of inbred rats. *Genetics* 26:157–158. (Abstr.)

Keiller, V. H. 1922. A contribution to the anatomy of spina bifida. *Brain* 45:31–103. Figs. 22.

Keller, W. 1941. Beitrag zur kausalen Genese von Kopfmissbildungen bei Säugetier und Mensch unter Berücksichtigung der neuen entwicklungsmechanischen Experimente. *Arch. J. Klaus-Stift.* 16:315–372. Figs. 8.

Kennel, J. 1901. Ueber eine stummel-schwänzige Hauskatze und ihre Nachkommenschaft. *Zool. Jahrb. Syst.* 15:219–242. Figs. 2.

Kerr, H. D. 1928. Some observations on the scapulae of the Chinese. *Arch. Int. Med.* 42:508–511.

King, H. D. 1931. Studies on the inheritance of structural anomalies in the rat. *Am. J. Anat.* 48:231–260. Figs. 2.

Koch, W. 1935. Neue pathogene Erbfaktoren bei Hunden. *Zeits. f. Abst. u. Vererb.* 70:503–506. Figs. 3.

Kudrjawtzewa, N. 1930. Über Marmorknockenkrankheit. *Arch. f. Klin. Chir.* 159:658–687. Figs. 17.

Kühne, K. 1931. Die Vererbung der Variationen der menschlichen Wirbelsäule. *Zeits. f. Morph. u. Anthrop.* 30:1–221. Figs. 185.

———. 1936. Die Zwillingswirbelsäule. *Zeits. f. Morph. u. Anthrop.* 35:1–376. Figs. 171.

Landauer, W. 1945. Rumplessness of chicken embryos produced by the injection of insulin and other chemicals. *J. Exp. Zool.* 98:65–77.

Lanier, R. R., Jr. 1944. Length of ribs in whites and negroes. *Am. J. Phys. Anthrop.* 2:137–146.

Lasker, G. W. 1945. Physical characteristics of Chinese. Harvard Thesis.

Lissner, Dr. 1885. Schwanzbildung beim Menschen. *Virchow's Arch.* 99:191–192.

MacDowell, E. C., Potter, J. S., Laanes, T. and Ward, E. N. 1942. The manifold effects of the screwtail mouse mutation. *J. Hered.* 33:439–449. Figs. 6.

Massaro, A. F. 1945. Vertebra plana (Calvé). *Radiology* 45:284–291. Figs. 9.

Matthews, W. 1889. The Inca bone and kindred formations among the ancient Arizonians. *Am. Anthrop.* 2:337–345. Figs. 6.

Meyer, W. 1939. Zur Kenntnis medial-schizosomatischer Früchte, ein Beitrag zur Frage des Status dysraphicus. *Zeits. Vererb. u. Konst-lehre* 32:189–215. Figs. 3.

Milles, B. L. 1928. *J. Hered.* 19:28.

Moehlig, R. C. & Murphy, J. M. 1935. Paget's disease (osteitis deformans). *Endocrinology* 19:515–522.

Mohr, O. L. & Wriedt, Chr. 1930. Short spine, a new recessive lethal in cattle; with a comparison of the skeletal deformities in short-spine and in amputated calves. *J. Genet.* 22:279–297. Pls. 3.

Morgan, T. H. 1903. The effect of lithium chloride on the development of the frog's egg. *Science, N. S.* 17:493–494.

Morrison, W. K. 1944. Bed-wetting and spina bifida. *Brit. Med. J.* ii. 830.

Myers, B. 1930. Spina bifida (two other cases in same family). *Proc. Roy. Soc. Med.* 23:603.

Nordby, J. E. 1934. Kinky tail in swine. *J. Hered.* 25:171–174. Figs. 3

Nowak, H. 1938. Die erbliche Trichterbrust. *Deut. Med. Woch.* 62:2003–2004.

Peiper, A. 1922. Ueber die Erblichkeit der Trichterbrust. *Klin. Wochens.* 1:1647.

Pepper, O. H. P. & Pendergrass, E. P. 1936. Hereditary occurrence of enlarged parietal foramina. *Am. J. Roentg. & Rad. Ther.* 35:1–8. Figs. 13.

*Petrovsky, S. G. 1934. Heredity of enuresis nocturna. *Soviet Psychoneur., Kharkov* 1:10–17.

Pirie, A. H. 1930. The development of marble bones. *Am. J. Roentgenol* 24:147–153. Figs. 8.

Pounders, C. M. 1935. Congenital osteosclerosis (marble bone). *Ann. Int. Med.* 8:966–971. Figs. 4.

Pryor, J. W. 1907. The hereditary nature of variation in ossification of bones. *Anat. Rec.* 1:84–88.

———. 1936. Ossification as additional evidence in differentiating identicals and fraternals in multiple births. *Am. J. Anat.* 59:409–423. Figs. 15.

———. 1939. Normal variations in the ossification of bones. *J. Hered.* 30:249–255. Figs. 4.

Ratcliffe, H. L. & King, H. D. 1941. Developmental abnormalities and spontaneous diseases found in rats of the mutant strain, stub. *Anat. Rec.* 81:283–305. Pls. 2.

Roberts, R. E. & Cohen, M. J. 1926. Osteitis deformans (Paget's disease of bone). *Proc. Roy. Soc. Med.* 19:13–40. Figs. 9.

Rutherford, W. J. 1934. Hereditary scoliasis. *Brit. Med. J.* ii. 87.

Sarpyener, M. 1945. Congenital stricture of the spinal canal. *J. Bone & Joint Surg.* 27:70–79. Figs. 12.

Saunders, R. L. de C. H. 1943. Combined anterior and posterior spina bifida in a living neonatal human female. *Anat. Rec.* 87:255–278. Figs. 10.

Sawin, P. B. 1945. Regional amplitude and specificity of influence of genetic factors inducing homoeotic variations in the axial skeleton of the rabbit. *Genetics* 30:20 (Abst.).

Schaeffer, O. 1892. Beitrag zur Aetiologie der Schwanzbildungen beim Menschen. *Arch. f. Anthrop.* 20:189–224. Pls. 2.

Schamburow, D. A. 1932. Die Vererbung der Spina bifida. *Arch. f. Rass. Biol.* 26:304–317.

Scheyer, H. E. 1934. Anthropological and roentgenological observations on the pelves of Chinese women. *Chinese Med. J.* 48:1228–1234.

Schultz, A. H. 1925. Embryological evidence of the evolution of man. *J. Wash. Acad. Sci.* 15:247–263. Figs. 16.

———. 1929. The metopic fontanelle, fissure and suture. *Am. J. Anat.* 44:475–499. Figs. 10.

Schultz, A. H. 1930. The skeleton of the trunk and limbs of higher primates. *Human Biol.* 11:303–438. Figs. 23.

———. 1938. The relative length of the regions of the spinal column in Old World Primates. *Am. J. Phys. Anthrop.* 24:1–22. Fig. 1.

Schwarz, Dr. 1912. Beitrag zur Kenntnis des geschwänzten Menschen. *Münch. Med. Wochens.* 59:928–929. Figs. 2.

Schwarzweller, F. 1937. Der angeborene Schulterblatthochstand und seine Beziehung zu den Missbildungen der Wirbelsäule. *Zeits. f. Vererb. u. Konst-lehre* 20:350–379. Figs. 12.

Sergi, G. 1886. Interparietali e preinterparietale del cranio umano. *Atti R. Accad. Med. di Roma* 9:117–156. Figs. 21.

Sernoff, D. 1902. Zur Frage über die morphologische Bedeutung der schwanzförmigen Bildungen beim Menschen. *Bull. Soc. Imp. Nat. Moscow* 15:232–258. Figs. 4.

Shaw, A. O. 1938. A skull-defect in cattle. *J. Hered.* 29:319–320. Figs. 3.

Shore, L. R. 1930. Abnormalities of the vertebral column in a series of skeletons of Bantu natives of South Africa. *J. of Anat.* 64:206–238. Figs. 13.

Shulman, B. H. 1942. Spina bifida with meningocele. *Arch. of Neur. & Psychiat.* 47:474–476.

Smith, E. M. 1934. Familial neurotrophic osseous atrophy. *J. Am. Med. Assn.* 102:593–595. Figs. 6.

Snyder, L. H. & Blank F. 1944. Bridged sella as a genetic trait. *Ohio State Med. J.* 40:318–320. Figs. 2.

——— ———. 1945. The inheritance of the shape of the sella turcica. *Ohio J. Sci.* 45:13–15. Figs. 2.

Snyder, L. H. & Curtis, G. M. 1934. An inherited "hollow chest." *J. Hered.* 25:445–447. Figs. 2.

Sozon-Iaroshevitch, A. 1926. The points of the architecture of osseus pelvis. *Russ. J. Anthrop.* 14:34–50. Figs. 8. (Russian with English summary.)

Stallworthy, J. A. 1932. A case of enlarged parietal foramina associated with metopism and irregular synostosis of the coronal suture. *J. Anat.* 67:168–174. Figs. 4.

Steiniger, F. 1938. Die Genetik und Phylogenese der Wirbelsäulenvarietäten und der Schwanzreduktion. *Zeits. f. Konst-lehre* 22:583–668.

Stibbe, E. P. 1929. Skull showing perforations of parietal bone, or enlarged parietal foramina. *J. Anat.* 63:277–278. Fig. 1.

Stockard, C. R. 1930. The presence of a factorial basis for characters lost in evolution. *Am. J. Anat.* 45:345–377. Col. Pl. 1, Figs. 6.

Stoddard, S. E. 1939. The inheritance of "hollow chest." *J. Hered.* 30:139–141. Figs. 2.

Stone, R. E. & Henriques, A. 1917. Three unusual cases of congenital origin. *Arch. of Pediat.* 34:512–515. Figs. 4.

Sweet, R. H. 1944. Pectus excavatum. *Ann. of Surgery* 119:922–934. Figs. 14.

Symmers, W. S. 1895. A skull with enormous parietal foramina. *J. Anat. & Physiol.* 29:329–330.

Thoms, H. 1937. Pelvic variations in 300 primiparous white women. *Surg. Gynec. & Obstet.* 64:700–704.

———. 1944. The obliquely ovate or Naegele pelvis. *J. Am. Med. Assn.* 124:294–296. Figs. 4.

Thoms, H. & Greulich, W. W. 1940. The comparative study of male and female pelves. *Am. J. Obstet. & Gynec.* 39:56–62.

Thomson, A. 1916. On the presence of genial tubercles on the mandible of man, and their suggested association with the faculty of speech. *J. Anat.* 50:43–74. Pls. 2. Figs. 15.

Tocantins, L. M. & Reimann, H. A. 1939. Peforating ulcers of feet, with osseous atrophy. *J. Am. Med. Assn.* 112:2251–2255. Figs. 3.

Troisier, J. & Monnerot-Dumaine. 1930. Thorax en entonnoir et doigt rentre. *Bull. et Mém. Soc. Méd. d. Hôp. de Paris* 46:311–318.

Turner, Sir W. 1885. The index of the pelvic brim as a basis of classification. *J. Anat. & Physiol.* 20:125–143.

———. 1886. The sacral index in various races of mankind. *J. Anat. & Physiol.* 20:317–323.

Valentin, B. 1931. Die kongenitale Schulterluxation. *Zeits. f. Ortho. Chir.* 55:229–240.

Vallois, H. V. 1932. L'omoplate humaine. *Bull. et Mém. Soc. d'Anthrop. Paris* 3:3–153. Figs. 70.

Van Creveld, S. & Heybroek, N. I. 1940. On Albers-Schönberg's disease (marble bones). *Acta Paediat.* 27:462–494.

Vilmorin, Ph. de. 1913. Sur les caractères héréditaires des chiens anoures et brachyures. *C. R. Acad. Sci. Paris* 157:1086–1089.

Voigt, R. 1937. Über die "Fenestrae parietales symmetricae." *Monatschr. f. Kinderhlk.* 70:224–231. Figs. 3.

Voorhoeve, N. 1924. L'image radiologique non encore décrite d'une anomalie du squelette. *Acta Radiol.* (*Stockh.*) 3:407–427. Pls. 3.

Waldmann, B. 1938. Beitrag zur Frage der Erblichkeit der spina bifida und der Rhachischisis. *Zeits. f. Vererb. u. Konst-lehre* 21:558–571. Figs. 2.

Warkany, J. 1944. Congenital malformations induced by maternal nutritional deficiency. *J. of Pediat.* 25:476–480. Figs. 3.

Warkany, J. & Nelson, R. C. 1941. Skeletal abnormalities in the offspring of rats reared on deficient diets. *Anat. Rec.* 79:83–100. Figs. 10.

Warkany, J., Nelson, R. C. & Schraffenberger, E. 1943. The malformations of the extremities. *J. Bone & Joint Surg.* 25:261–270. Figs. 6.

Weber, F. P. 1935. Hereditary large parietal foramina. *Proc. Roy. Soc. Med.* 29:122–125. Figs. 3.

Weber, F. P. & Huber, H. 1939. Beitrag zur Ostitis deformans (Paget). *Deut. Arch. Klin. Med.* 184:78–84. Figs. 9.

Weidenmüller, K. 1936. Beitrag zur Frage der Erbbedingtheit der Spina bifida. *Zeits. f. Vererb. u. Konst-lehre* 20:42–65. Figs. 12.

Weissenberg, S. 1928. Zur Stammbaumkasuistik. *Arch. f. Rass. Biol.* 20:428–432.

Wilcox, L. F. 1932. Osteopoikilosis (disseminated condensing osteopathy). *Am. J. Roentgenol.* 27:580–584. Figs. 7.

Williams, C. T. 1872. Congenital malformation of the thorax; great depression of the sternum. *Trans. Path. Soc. Lond.* 24:50–52.

Williams, H. U. 1929. Human paleopathology, with some original observations on symmetrical osteoporosis of the skull. *Arch. Pathol.* 7:839–902. Figs. 18.

Wilson, A. K. 1944. Roentgenological findings in bilateral symmetrical thinness of the parietal bones (senile atrophy). *Am. J. Roentgenol.* 51:685–696. Figs. 5.

Windholz, F. 1932. Über familiäre Osteopoikilie und Dermatofibrosis lenticularis disseminata. *Fortschr. Roentgenstr.* 45:566–582. Figs. 18.

Wriedt, C. & Mohr, O. L. 1928. Amputated, a recessive lethal in cattle. *J. Genet.* 20:187–215. Figs. 3.

Ziesch, H. 1925. Statistisch-genealogische Untersuchungen über die Ursachen der Rachitis, insbesondere ihre Erblichkeit. *Arch. f. Rass. u. Ges. Biol.* 17:61–81.

Chapter XIII

METABOLIC DEFECTS AND DERANGEMENTS

IN ALL cases of inborn deranged metabolism the probable cause is the lack of an enzyme, in the absence of which a chemical step is missed and some normal metabolic change fails to take place. In 1932, Krebs and Henseleit showed that in the mammalian liver the stages of urea formation were ornithine → citrulline → arginine → urea. Srb and Horowitz (1944) have recently shown that the ascomycetous fungus, Neurospora, synthesizes arginine in the same three stages. The enzyme arginase controls the last step, and inability to synthesize arginine is inherited as a single gene. By means of X-rays they obtained seven arginineless strains and concluded that there are at least seven steps in the synthesis of arginine from sugar and ammonia, each controlled by a different gene. They similarly found at least two steps in the synthesis of citrulline from ornithine. Using similar methods, Beadle and Tatum (1941) had previously obtained mutants which failed to synthesize pyridoxine, thiazole and p-aminobenzoic acid respectively, these conditions segregating in crosses as single gene differences. Another mutation of Neurospora (Tatum, Bonner and Beadle, 1944) fails to transform anthranilic acid into tryptophane. In later work, summarized by Horowitz et al. (1945), about 100 gene mutations have been produced which are concerned with a particular stage in the synthesis of a vitamin, an amino acid or a component nucleic acid. The synthesis of various essential chemical constituents of protoplasm is thus shown to be under genic control.

Similarly in animals, the presence of xanthophyllase in rabbits determines the inheritance of yellow fat, and the presence or absence of amylase in silkworms is similarly inherited. Many enzyme differences controlling pigment formation in flowers and in the coats of animals are well known. In rabbits, the ability to produce the enzyme atropinesterase, which hydrolyzes atropin in the serum, is due to a partially dominant gene which is linked with a factor causing extension of black in the coat (Sawin and Glick, 1943).

Most of the cases of enzyme absence in man are extremely rare, and Sir A. Garrod (1923) has summarized our knowledge of their nature and their inheritance. He includes under this head albinism (Chap. IX), alcaptonuria, cystinuria (and diaminuria), porphyrinuria, haematoporphyria, steatorrhoea, and pentosuria. They are all inherited as recessive conditions, usually in sibs with normal parents, and as they marry normals, their children are usually immune. They are, however, much commoner in men than women, but temporary alcaptonuria occurs in women, and toxic porphyrinuria due to sulphonal is almost confined to women. Macklin (1934) surveyed the later work on inherited anomalies in metabolism, and Duncan (1942) considers at length the physiological and clinical aspects.

Wollaston discovered *cystine* in bladder calculi in 1810. Only 107 cases were reported in the century following. It is usually diagnosed by the presence of hexagonal plates of cystine in the urine and has been estimated to occur with a frequency of 1 in 15,000–35,000 persons. New methods of testing (Patch, 1934) give a frequency of 29 cases in 11,000 or 1 in 380. Among over 10,000 students (6253 ♂ 4281 ♀) tested at Michigan University (Lewis, 1932), 3 ♂ and 1 ♀ showed cystine crystals in the urine and positive chemical tests were obtained repeatedly in 14 others. This is a frequency of 1 in 585 persons. No calculi were known in any of these cases. It thus appears that healthy young people occasionally excrete cystine regularly in small quantities. It is normally found in the blood as a product of digestion. If the necessary chemical tests were made in urinalyses, the familial occurrence of this mild symptomless form would probably be found.

A severe form of cystine diathesis was found by Abderhalden (1903) in a family with grandfather, father and all five children affected. Three of them, who died as infants, had cystine in their tissues, the others had cystinuria. In this family the condition was dominant. Lignac (1925) described four cases of young children with renal rickets, dwarfism and deposits of cystine crystals. In a later paper (1938) he added three more cases of *renal dwarfism* with cystic kidneys and cystine deposits in spleen and kidneys. He recognizes infantile (fourteen months) and juvenile (sixteen years) forms of the disease. The disturbed cystine metabolism may be the primary cause of the renal conditions. Russell and Barrie (1936) described two sisters who died as children with renal rickets and dwarfism, Brights' disease, glycosuria and cystine storage in the reticulo-endothelial system. The parents and six sibs were normal.

A boy with healthy parents and two healthy sibs died with cystinuria and chronic nephritis, without cystine storage. Another boy of thirteen in another family died with the same symptoms, having had cystine calculi removed years before. A similar case is described by Beumer and Wepler (1937). Graham and Hutchinson (1941) found four cases of renal dwarfism in a family of eight children whose parents were normal. This appears to be a case of recessive chronic interstitial nephritis. Danis and Rossen (1941) describe the condition in brother and sister. They found at least ninety cases reported, with an average age of seven years.

One pedigree of cystinuria in a Scottish family, with twelve cases in two generations, has repeatedly been published. Thin (1929) described the family, in which three cousin marriages occur, and Robson (1929) studied the protein metabolism and compiled the pedigree (Fig. 186). Kretschmer (1916) reported cystinuria and cystine lithiasis in twin brothers, and Patch recorded cystinuria in two brothers. In another family, two normal and unrelated parents had three children, all with cystinuria. Probably, as Punnett suggests, two independent factors must be present to produce cystinuria, but further evidence of the method of inheritance is needed. Pierce (1934) reported a brother and sister in Manitoba with cystine calculi. No cystine crystals could be obtained from the urine either before or after the operation on the sister, but there was a high amount of neutral sulphur in the urine.

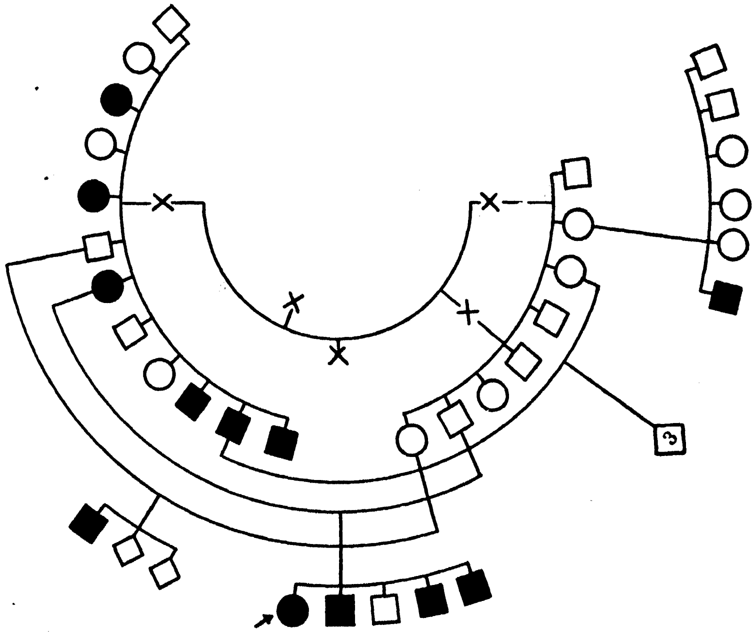

Fig. 186. Pedigree of cystinuria. (After Robson)

Graves (1922) found renal calculi of pure cystine in a Russian woman and an American man. He points out that, unlike most renal calculi, these throw little or no X-ray shadow.

Oxalic Urinary Calculi

Kidney and bladder stones are generally considered to be the same disease. Younger people tend to have the former (nephrolithiasis) and older ones the latter; the average age for onset of renal stones is thirty-nine and for bladder stones fifty-one years. Gram (1932) described a family with the very rare condition of calcium oxalate urinary calculi. The method of inheritance is also of great interest, as shown by Figs. 187 and 188. The condition is a sex-limited dominant with low penetrance, but normal (heterozygous) females can transmit, i.e., the condition is autosomal but irregularly dominant in the male and completely recessive in the female.

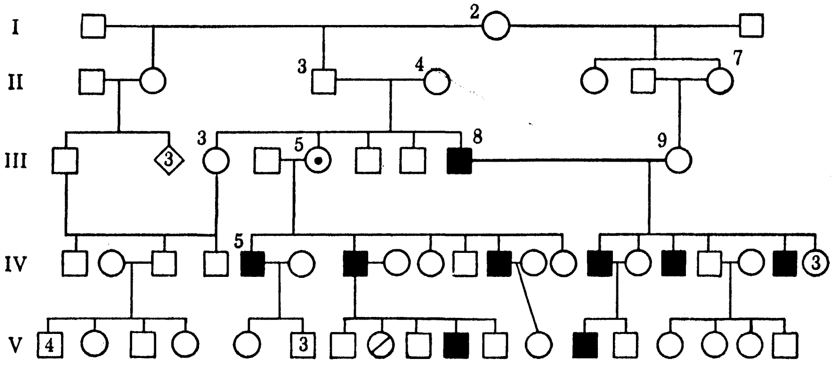

Fig. 187. Pedigree of oxalic urinary calculi. (After Gram) See text.

Gram suggests that II. 4 (Fig. 187) was a carrier in the X-chromosome, but this is unnecessary if dominance is irregular in the male. The inheritance clearly came from II. 4, and not from I. 2, who was married twice. Her descendants by both marriages are free from the condition. Heterozygous females are normal but transmit, as shown by III. 5. In addition to those shown in the pedigree, II. 7 had three generations of descendants, a total of 49♂ and 31 ♀, all normal. Hence II. 7 could not possibly have been carrying the gene for oxalic calculi. Cases I. 1 and II. 3 lived to old age and had no stone. Cases I. 1 and I. 2 had, besides those shown in the pedigree, a total of 41♂ and 24♀ descendants in four generations, all normal. One case of "renal gravel" in the fourth generation must have been extraneous. Incidentally it will be noted that throughout these pedigrees there is a remarkable excess of sons over daughters. The condition then evidently was transmitted by II. 4 only.

Figure 188 traces the descendants of the woman (III. 5 in Fig. 187). Her grandmother, I. 2, died at the end of the eighteenth century. Her uncle (II. 2) had four generations of descendants, with a single case of calcium oxalate calculi in the fourth generation. In this pedigree, which shows fifteen affected males in four generations, there are five cases of transmission through normal males, three through affected males and four through normal females. These pedigrees look very much like a sex-linked recessive with crossing-over between the X- and Y-chromosomes. But the fact that normal males transmit rules this out.

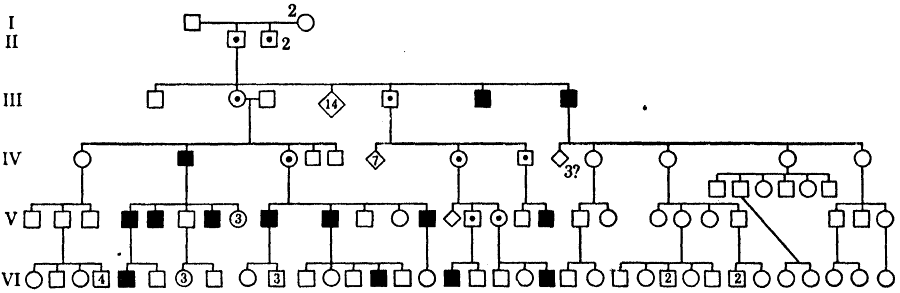

Fig. 188. Inheritance of oxalic urinary calculi in descendants of III. 5, Fig. 187. (After Gram)

The excretion of oxalic acid in the urine of men and dogs was studied by Wesley Mills as early as 1885.

Alkaptonuria is characterised by the presence of alkaptan (probably a derivative of tyrosin) in the urine. Due to the absence of an enzyme, the amino acids, phenylalanine and tyrosin, are not completely destroyed in the body. The urine becomes dark on standing or on the addition of alkali. Their presence causes arthritis and the deposition of pigment in the cartilages and homogentisic acid is excreted in the urine. Garrod recorded alkaptonuria in twelve families, in six of which the parents were first cousins. In six families two children were affected, in four families three and in two families four. In one family two brothers of the patient, three daughters and one grandchild were affected. Bateson suggested in 1902 that the condition is a Mendelian recessive and this is confirmed by all the above families, with one exception where it appears to be dominant. Charts compiled by Toenniessen (1922) show 23 normal : 8 affected in three sibships. In one mating RR × DR there were four with alkaptonuria and four without it. Pomeranz *et al.* (1941) found only a hundred cases reported. However, about 122 cases were recorded up to 1929 (Bagnall), mostly in Europe. Pieter's pedigree (1925) contained 13 cases (10 ♂ 3 ♀) in four generations and is strictly dominant, the sibships numbering 11 affected : 9 normal. Hogben, Worrall and Zieve (1932) have compiled and analyzed all the cases. In three or four families it may be dominant, but the remaining forty-five are recessive. Affected males in all the records of Hogben number 72, affected females 37, almost exactly a 2 : 1 ratio. Abbott (1941) finds the condition in a Negro family in Virginia (Fig. 189). The mother was dead, but she was probably not alkaptonuric. Gould and Thomas (1943) devised a quick test for alkaptonuria. The urine is made strongly alkaline with caustic soda or caustic potash. A drop is then placed on sensitized photographic paper, which turns black instantly.

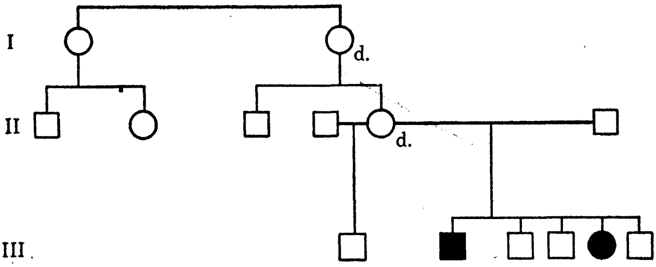

Fig. 189. Alkaptonuria in a Negro family. (After Abbott)

Ochronosis with alkaptonuria is a nearly related condition described by Virchow (1866). In this rare condition the skin, cartilage and fibrous tissues are colored gray or black and the urine becomes dark. It is recessive, relatively harmless and may also occur without alkaptonuria. Staining of the cartilage evidently results from the metabolic derangement. Osler (1904) described two brothers with coal-black nose and cheeks, blue-black ears and deep black sclerotics where exposed. Pomeranz, Friedman and Tunick (1941) reported two cases in men, with the triad alkaptonuria, ochronosis and arthritis. It usually develops very slowly in middle life and can be produced by phenol poisoning.

Some rabbits contain in their blood an enzyme, atropinesterase, which destroys atropin. Sawin and Glick (1943) find this condition inherited as a single gene linked to the factor for extension of black pigment in the coat. It appears about one month after birth and shows incomplete dominance, females also containing more of the enzyme in their blood than males. The demonstration that the presence of a particular enzyme is controlled by a gene is significant and probably applies to many enzymes.

Pentosuria, a chemical anomaly in which pentose sugar is excreted in the urine, is a condition which is found almost exclusively among Jews. It has no detectable influence on health. Chronic pentosuria was first reported by Salkowski and Jastrowitz (1892). Margolis (1929) found seventy-eight cases in the literature, twenty-seven in Jewish families, two in Greeks, two in English, the race not being mentioned in the others. He described the condition associated with migraine in a Jewess whose father, mother and sister had migraine only.

Pentosuria has generally been described in single cases, or occasionally in two sibs, and once in father and son. Jones and Nissler (1925) reported five cases in one Jewish family. Garrod gives a pedigree in three generations and the condition cannot always be recessive (Macklin, 1934). Although generally regarded as a harmless metabolic anomaly, 90 per cent of the cases have nervous symptoms; it is frequently associated with migraine and a vagotonic constitution. Of the reported cases, twenty-four occurred in nine families and twenty-seven were Jewish. The sex-ratio of affected persons was 48 ♂ : 25 ♀, but it is probably exaggerated, as many cases in men are discovered through examination for life insurance. This might also apply to alkaptonuria.

The forms of pentosuria are sometimes classified as (1) alimentary, (2) chronic, (3) associated with diabetes mellitus. Eating apples or other fruits will produce the condition temporarily. In the chronic type pentose may be present for months or years and is not markedly affected by diet. Marble (1932) discovered three cases in a group of 9000 renal glycosuria patients. They were Jewish males two of whom had relatives with diabetes mellitus. By 1940 the number of cases had increased to nine. Enklewitz and Lasker (1933) described twelve cases, noted reports of a hundred others and found that the pentose sugar excreted was l-xyloketose in all cases. Lasker, Enklewitz and Lasker (1936) recognize at least two types of chronic essential pentosuria, one excreting dl-arabinose and the other l-xyloketose. They found thirty-seven cases of *xyloketosuria* in twenty families, all in accord with a simple recessive inheritance and nearly all in Jews. The gene is very rare in the population, but eight cases were found in one family. Moss and Walker (1942) describe a case of pentosuria with diabetes mellitus in a non-Jewish woman as an excessively rare medical curiosity.

Cammidge and Howard (1926) reported *arabinosuria* in father and son and, in another family, in uncle and nephew, which suggests an irregular dominant inheritance.

Essential fructosuria is another rare metabolic condition, not a disease but a harmless disturbance of metabolism. Van Creveld suggested that it is a remnant of foetal life, as newborn children have less tolerance of fructose. Heeres and Vos (1929) describe the case of a girl in Holland. The condition disappears if there is no fructose in the food, but when fructose is taken in fruit or honey only about 14 per cent is excreted. Its presence in the urine shows lack of ability to convert it into glycogen, perhaps combined with increased permeability of the kidneys to laevulose. Special tests are necessary to distinguish fructose from the more usual glucose. Silver and Reiner (1934) report six cases, two of them brothers, all seen in one year. They regard it as a specific enzymatic deficiency.

Two Jewish brothers are described by Jacobsen (1940). Their case had been diagnosed as diabetes, but their carbohydrate metabolism was normal. Lasker (1941) reviewed the subject, finding only forty true cases recorded. Its rarity is estimated at less than 1 in 130,000 persons. It occurs in sibs, the parents are frequently related and various pedigrees show that it is a simple recessive. Other references to inherited sugar anomalies may be found in Bock (1944).

Tyrosinosis was discovered by Medes (1932) in a Russian Jew in Minneapolis with myasthenia gravis. He excreted daily 1.6 g. of p-hydroxyphenyl pyruvic acid in the enol form. The condition is very rare, as shown by the examination of urine containing 0.3 per cent sugar from 14,753 life insurance applicants without finding another case. A single case of alkaptonuria was found. This Russian had no abnormal pigmentation. Normal persons oxidize tyrosine via p-hydroxyphenyl pyruvic acid or via 2:5-dihydroxyphenylalanine. Both lead to 2:5-dihydroxyphenyl pyruvic acid and thence to homogentisic acid. In this man there is a block at the p-hydroxyphenyl pyruvic acid, which is excreted, as well as its reduction product, together with tyrosine and its oxidation product, l-3:4-dihydroxyphenylalanine. There is no mention of relatives, but this is probably another case of simple recessive inheritance. The gene must be very rare. Blatherwick (1943) examined over 26,000 more in New York without finding another case.

Tryptophanuria has been found (Brice, 1932) occurring both by itself, indicating some derangement of protein metabolism, and in association with *albuminuria*. Among eighty cases of dementia praecox, eight showed tryptophanuria. The significance of this and the possible inheritance of the condition remain to be determined.

Steatorrhoea is an extremely rare defect in fat metabolism, apparently due to a deficiency of the pancreatic secretion. Tulpius observed the condition in the seventeenth century and suggested that it was connected with disease of the pancreas. The first modern case was described in 1911. Two affected brothers were in a family of five children from a cousin marriage (Hurtley and Garrod, 1913). The affectee passes liquid fat which solidifies on cooling, but has no other morbid symptoms. Another boy occurred in a family of three whose parents were unrelated (Miller and Perkins, 1920). A recessive gene is again indicated.

One boy grew up in active work and adjusted his diet so that "butter stools" were seldom passed. Soecknick and Thoenes (1927) described two boys and a girl whose parents were first cousins. Cockayne (1933) described a girl of twelve whose parents were unrelated. He found only 5♂ and 2♀ cases recorded. Thaysen (1935) described ten cases of idiopathic steatorrhoea in Denmark and referred to another. These cases included a brother and sister in one family and two sisters in another. He finds this metabolic derangement characterised by (1) a quantity of fat in the faeces, (2) a flat blood-sugar curve, (3) a raised rate of basal metabolism, with diminished absorption of fat in the food. He concludes that coeliac disease and non-tropical sprue are the same disease under other names.

Konstam and Gordon (1936) describe a case of acquired steatorrhoea in a man of fifty-five. O'Donovan *et al.* (1942) show that steatorrhoea can be induced by infestation with the intestinal parasite *Giardia lamblia.* A man in Dublin died of giardiasis and the symptoms of steatorrhoea. In a boy of nine with the same symptoms the parasites were destroyed and he recovered. But a year later X-ray photographs showed a persisting abnormality in the epithelium of the small intestine, caused by the action of the parasite. Some cases of supposed idiopathic steatorrhoea may therefore be of this nature. Bennett *et al.* (1932) studied fifteen cases of adult steatorrhoea resulting from gastro-intestinal dysfunction, a nutritional disturbance associated with tetany, osteomalacia and anaemia. Steatorrhoea and a disturbance of calcium metabolism are common to all, together with bone changes (osteoporosis and rickets). More attention needs to be paid to the inheritance factor in all these cases. Moore *et al.* (1936) investigated ten cases of idiopathic steatorrhoea at ages nineteen to sixty-three years. They suggest that non-tropical sprue or idiopathic steatorrhoea be known as *Gee-Thaysen disease.* It is frequently accompanied by anaemia, osteomalacia with subcalcification of bone, deformity (Fig. 190) and kyphosis. Gee's coeliac disease, described in 1888, is believed to be the same and should be called *Gee-Herter disease*, the term *sprue* being confined to the tropical disease. This leaves *steatorrhoea* as the name for the inherited form of deranged fat metabolism alone.

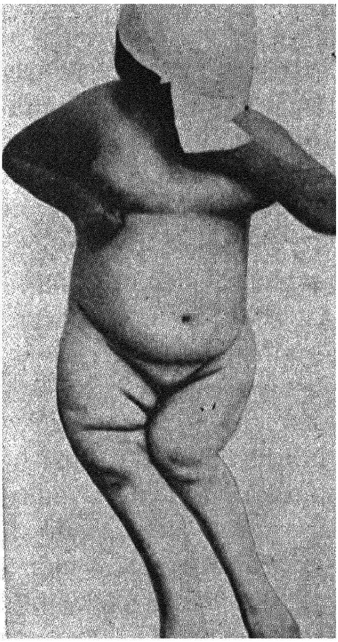

Fig. 190. Idiopathic steatorrhoea (Gee-Thaysen disease). (After Moore *et al.* 1936)

Mogensen (1937) described three cases of idiopathic steatorrhoea and concludes that the derangement can be induced by living in the tropics, by pregnancy and by other conditions. Obstruction of the lacteals will produce it. Harper (1938) characterizes the distinctions between congenital pancreatic steatorrhoea and coeliac disease.

Porphyria, a condition which is frequently known as *hematoporphyria*, is a disturbance of the pigment metabolism in man and some animals. The latter name should be dropped, as hematoporphyrin is a laboratory product and not a natural secretion. In porphyria the urine is reddish brown or Burgundy color and the skin is abnormally sensitive to light. The teeth and bones may also be colored red or brownish. The porphyrins are the "building blocks" out of which hemoglobin is formed in animals and chlorophyll in plants. The chemistry of the porphyrins and the related bile pigments is dealt with by Rimington (1939). They play a vital role in pigment metabolism. The pigment in the eggshells of birds consists largely of protoporphyrin; the feathers of some birds contain uroporphyrin III and in others coproporphyrin III.

Congenital porphyria is rare and is generally recessive in inheritance. Minute traces of coproporphyrin are normally present in the urine. Günther, in 1911, was first to recognize this inborn error of metabolism, and Hans Fischer showed that in congenital porphyrinuria the main portion in the urine is uroporphyrin while coproporphyrin is present in the faeces. Protoporphyrin may also be present as a degradation product of hemoglobin. Mackey and Garrod (1922) referred to the case of two fisherman brothers from the Island of Lewes in the Hebrides, described in 1892. Their skin was scarred where exposed, they had red urine and hydroa aestivale (irregular red patches forming on the skin, with itching vesicles). There were four normal sibs and a girl who may have died with the same complaint. These authors cite a probable case in Germany in 1874 and one in France in 1896. Three later cases were described in Germany, one in Italy and one in Denmark, and Mackey and Garrod add another case. This boy of six was later (1926) more fully investigated. He was bright and intelligent, of average size, but excreted porphyrins. By avoiding bright light and by the use of fluorescent ointments, mutilations of his hands and face could be avoided. Ashby (1926) described a girl of four with remarkable red teeth and urine of a port wine color. The bones were pigmented like the teeth, but there was no enlargement of liver or spleen. Gray (1926) described a girl of eighteen, the only case in a family of seven, the parents being first cousins. She had red urine and blisters began on her skin at five years of age, forming ulcers which left scars when they healed. In some cases the colored bones throw a shadow when the hand is held before a strong light.

Porphyrinuria can be produced by the administration of such drugs as sulphonal and phenacetin.

Mason, Courville and Ziskind (1933) recognized four types of porphyria; (1) chronica, (2) congenita, (3) acuta toxica and (4) acuta idiopathica. The second and last are inherited. About four times as many males as females are affected. Their condition is constitutional. The skin becomes red on exposure to light, then vesicles appear. Many die in early life if exposed to strong light. These authors made a clinical study of four cases. The nature of the defect is still obscure. According to one view it is a product of abnormal hemoglobin katabolism, but it more probably represents a reversion to a more primitive level of pigment formation through lack of specific enzymes. Macklin (1934) saw two families in which three of seven children were afflicted; two with a single affected child; another in which first cousins were victims; and one in which two children and their cousin had the disease. In the six families there was no known consanguinity. Turner (1938) regards porphyria in the tissues as the persistence of a foetal pyrrole metabolism.[1] He investigated a family in which two of the five daughters were affected (evidently recessive) and found a red-brown pigment called *urofuscin* to be excreted also in large amounts. Some fifty cases were known in 1933. Radaeli (1911) records the only case in father and son. Nesbitt (1944) shows *acute porphyria* in three women in one family (two sisters and a paternal cousin), and the paternal grandfather was also affected. Irregular dominance is indicated in this family.

Waldenström (1937) wrote a large monograph on porphyria with an extensive biochemical investigation of nineteen families. His criterion was the presence of uroporphyrin or porphobilinogen in the urine. The condition evidently differed from the recessive form hitherto considered. Symptoms developed at about thirty years of age, there was no photosensitivity of the skin nor color in the bones, but the acute porphyrinuria was followed by paralysis and death. One pedigree contained 7 cases (4♂ 3♀) in two generations, with fourteen normal sibs. In another the grandfather, father, three daughters and three of their ten children as well as a distant cousin were affected. In several families the affected were all in one generation — four sisters, two sisters and a brother, three sisters, four daughters and two sons, two brothers, etc. The dominance is often irregular and *possibly* two factors are involved. This appears to be in some respects an exception to the rule that the dominant form of a disease gene is milder than the recessive form, for the inheritance was shown to be essentially dominant in eight families.

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[1] Using spectroscopic methods, Klüver (1944) has shown the widespread occurrence of a coproporphyrin in the central nervous system (white matter) of mammals and birds. This helps to account for the wide variety of nervous and mental symptoms accompanying porphyria. He suggests that certain neurological and psychiatric disorders are associated with cerebral porphyria.

In addition to the records of Europeans, porphyrinuria has been described in Japanese families but differing in certain respects. Affected babies are born with enlarged spleen and soon develop anaemia, dying between six and eighteen months of age (Cockayne, 1933). A number of isolated cases have been described, which are probably recessive outcrops.

That the same mutation can occur in cattle has been shown by Fourie and Rimington (1937). In a herd in South Africa twelve cases were found, apparently recessive, some of them in the offspring of a particular bull and his daughter. In a black-and-white cow of another herd, only the white areas showed lesions from photosensitization. Clare and Stephens (1944) report porphyria in pigs in New Zealand. An affected sow produced, by two normal boars, 5 affected : 8 normal pigs, hence probably dominant. Figge (1944) shows that the harderian or accessory lacrimal glands are red fluorescent in mice, rats and hamsters, owing to the secretion of porphyrins, but not in other mammals, birds or reptiles. These three animals are most susceptible to carcinogenic agents. This supports the view of a direct relation between porphyrin metabolism and cancer susceptibility.

In *hydroa vacciniforme* the skin conditions resemble those of porphyrinuria but there is little or no porphyrin in the urine and the skin is less severely affected. As in porphyrinuria, more males than females are affected and it remains uncertain whether the two conditions are genetically distinct. Hydroa without porphyrinuria is also dominant in some families and recessive in others (see Siemens, 1922). Radaeli (1911) described three cases, including a father and child of eleven years, hence probably dominant.

Hemochromatosis: This condition was named in 1899 by von Recklinghausen. It is frequently called *bronzed diabetes* and is a very rare disease, probably due to an error in iron metabolism which affects every cell. Sheldon (1934) made a study of 7 cases and found 304 in the literature. It is characterised by the production of melanin, especially in the smooth muscle, connective tissue and skin, and also by the formation of an iron compound, hemosiderin, in all the tissues. There is no disturbance to health, except that cirrhosis of the liver, pancreas, spleen and other organs develops. Usually the symptoms only appear in middle life and in the later stages they are generally accompanied by diabetes mellitus. The earliest account of a case was by Hanot and Chauffard (1882). Frisch (1922) described a "black family" in Vienna in which seven siblings and their mother were pigmented. Althausen and Kerr (1933) concluded that two conditions are necessary for its development: (1) a constitutional predisposition of the liver, (2) chronic intoxication affecting the susceptible organ. Alcohol is the most frequent agent and copper is perhaps another. Darnall (1935) described three cases and regards the triad, grayish-brown pigmentation of the skin, liver cirrhosis and diabetes mellitus as characteristic. Lawrence (1935) gives a pedigree of two cases (Fig. 191) from which it is evidently recessive and associated with glycosuria and diabetes. Sheldon (1935) has written a comprehensive work on the subject. Hemofuscin, a brown iron-free pigment probably related to melanin, is also produced. Males appear to be much more frequently affected than females.

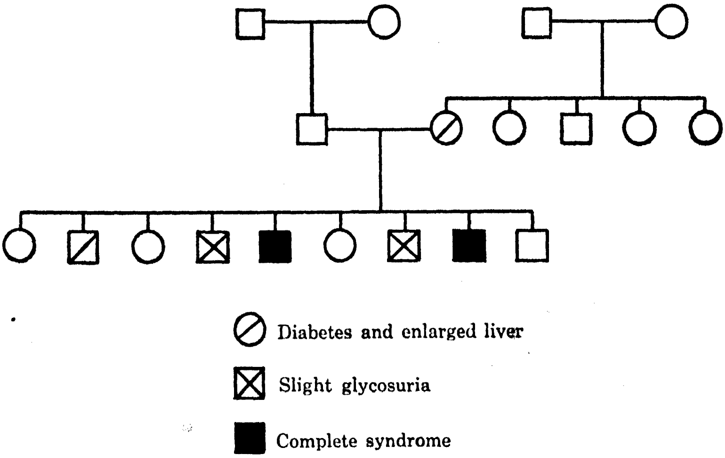

Fig. 191. Pedigree of hemochromatosis (bronzed diabetes). (After Lawrence)

Urobilinuria: Steensma (1914) reported an extraordinary family (Fig. 192) with 17 cases (10♂ 7♀) in four generations. The urine was free from urobilin if the patient were lying down, but contained it if excreted in an upright position. Steensma suggests that, as the posture affects the excretion, there is some anatomical defect. He postulates a ductus venosus not completely obliterated, so that blood from the intestine can escape into the general circulation through the old foetal route, the upright posture favoring passage through the ductus venosus. The inheritance is that of an irregular dominant. In three cases there is transmission by supposed normals, but two of them, who were dead, might have been affected. Case III. 13 however was certainly normal and transmitted the gene.

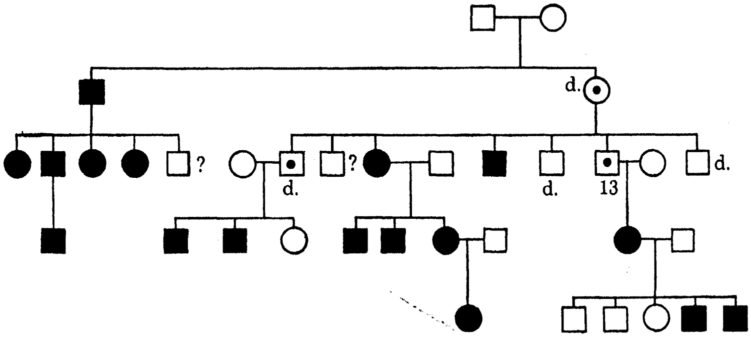

Fig. 192. Pedigree of urobilinuria. (After Steensma)

For *phenylketonuria*, recently discovered in dementia praecox patients, see p. 1088.

Albuminuria can be produced by many functional conditions or as a part of various syndromes. Dickenson (1875) gives a pedigree of albuminuria showing eleven cases in three generations. The inheritance is evidently dominant. Portraits of ancestors of this family as far back as the Wars of the Roses are said to show a characteristic clear, transparent pallor like modern members.

Haematuria can of course be produced by many conditions. Guthrie (1902) published a pedigree of haematuria showing its inheritance (as a Mendelian dominant), with twelve cases in three generations. The condition in this family was not postural, could occur by day or night, and was regarded as representing a congenital weakness or varicosity of the walls of the renal vessels. Hurst (1923) regards *haemorrhagic nephritis* as a better term for this condition, because often only traces of blood were present in the urine, while there was much albuminuria, the haematuria being intermittent, but albumen present between the attacks. His pedigree (Fig. 193) shows sixteen cases in three generations, the inheritance an irregular dominant. Individuals with albuminuria are marked A. Number II. 3 had epistaxis and haematemesis. The condition was more severe in some, slight in others, but it evidently increased from youth to adulthood. Haematuria could be brought on by eating strawberries or asparagus, and in several women, but not in men, by black currants or claret. Hurst also cites Benson's case with four individuals in a family having acute nephritis developed from oedema and albuminuria; Atlee's case of three sisters with albuminuria and intermittent haematuria, the father dying of uraemia; and

Fergusson's case in which father, mother, and eight children all had albuminuria. There appear to be no recent studies of the inheritance of these conditions.

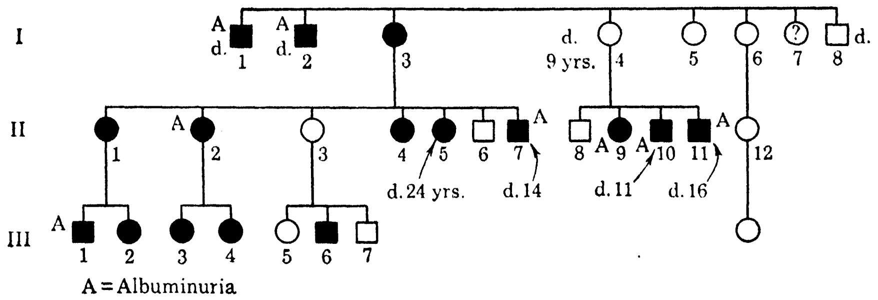

Fig. 193. Pedigree of haemorrhagic nephritis. (After A. F. Hurst)

Von Gierke's Glycogen Disease

This very rare condition was described by von Gierke (1929) from a postmortem study of two children. Forty cases had been reported up to 1938. It is characterised by a disturbance of glycogen metabolism. There is an accumulation of this substance in the liver, heart, kidneys and other organs in infancy. The heart may be enlarged to five or six times its normal size, but the spleen is not affected. The condition appears to be congenital. Two or three cases in a family have been reported several times. Smith and O'Flynn (1933) described a brother and sister with enormous liver and pigmented skin, the histological character of the liver cells being highly abnormal. In von Gierke's cases the kidneys also were enlarged. Warner (1933) recorded the condition in a girl two years old. Another child in the same family died at five months probably from the same disease. Lindsay, Ross and Wigglesworth (1935) described a French-Canadian boy and there are many other single cases. Ellis and Payne (1936) give a full bibliography and describe two families. In one, a brother and two sisters were affected; in the other, two sisters and possibly the brother. There were no normal sibs in either family, but the mother of the second family was found postmortem to have a greatly enlarged liver. This

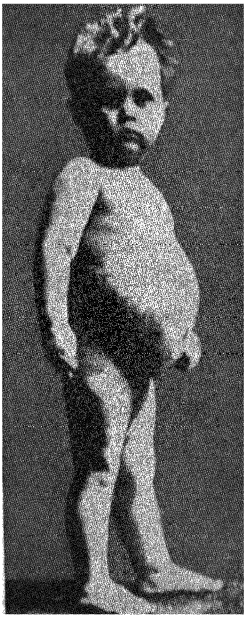

Fig. 194. Von Gierke's glycogen disease in child. (After Ellis and Payne)

is probably an expression of the heterozygous condition. In twenty-five families involved there were two cousin marriages, so all the evidence clearly indicates a simple recessive gene. Affected children (Fig. 194) show obesity and a lack of growth and of sexual development, suggesting anterior pituitary dysfunction. Gardner and Simpson (1938) record two exceptional cases of sudden death from glycogen disease in an infant and a boy of eleven. In the latter, the heart was three times the normal size and the liver was slightly enlarged but no other organ was affected. Von Gierke and van Creveld both suggested that glycogen disease is a continuation of the foetal condition of the liver. The latter (1939) has made an extensive study of the various glycogen diseases and their pathogenesis, with full references to the literature. The basic defect may be the absence of amylase from the liver cells.

Gaucher's Disease

There are four hereditary diseases involving derangements of lipoid metabolism and with many points in common, including yellow patches (xanthomata) on the skin and splenomegaly. They are: 1. Gaucher's disease, in which kerasin accumulates. 2. Schüller-Christian disease, a disorder of cholesterin metabolism. 3. Xanthomatosis, also a disorder of cholesterin metabolism. 4. Niemann-Pick disease, a disorder of phosphatide metabolism. Gaucher's disease was named after an eminent French dermatologist, who described it in 1882. Splenomegaly is a constant feature and the liver is often enlarged too, accompanied by anaemia. The age of onset ranges from birth to thirty-two years, the disease advancing very slowly and it may extend over thirty or forty years. Kerasin belongs to the cerebrosides, containing nitrogen but not phosphorus. It does not stain with lipoid stains such as Sudan and is very inert chemically. The kerasin accumulates chiefly in the spleen, liver and bone-marrow, forming characteristic "Gaucher cells" which can be found by splenic puncture and look hyaline and homogeneous. There is also symmetrical pigmentation (xanthoma) of the legs (Fig. 195), while in hemochromatosis the legs are usually normal. The disease often occurs in Jews and is often accompanied by a malar flush and myopia. Gaucher's and Niemann-Pick disease have recently been ascribed to a primary disturbance of the reticulo-endothelial system.

Brill, Mandelbaum and Libman (1905) recorded a family of four affected sibs and described one of them in detail. Reiss and Kato (1932) reported three cases, in two of which it was fatal, in a Japanese family in California with three normal sibs. The inheritance is evidently recessive. Hoffman and Makler (1929) tabulated nearly ninety cases in the literature. The first male case was described by Brill, Mandelbaum and Libman (1905), three sisters and a brother. Patients often show increasing anaemia, emaciation and finally death, splenectomy being the only known treatment. Anderson (1933) described a Russian family with four or five affected sisters, their father's mother and her two sisters being also probably affected. The reason for the great excess of female cases is not clear. Bloem, Groen and Postma (1936) described five unrelated cases in adults, four of them Jews. Emanuel (1941) reported two unrelated cases and points out that the familial disease may take a benign course. In a malignant form the central nervous system is involved and death in infancy usually occurs.

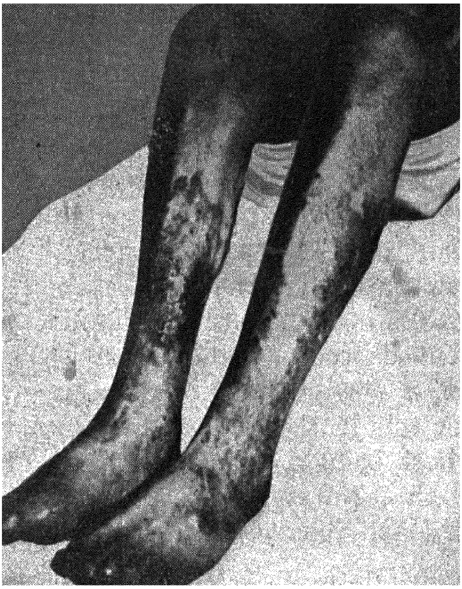

Fig. 195. Symmetrical pigmentation of the legs in Gaucher's disease. (After Bloem, Groen & Postma)

Leesmith (1933) described three boys in a family of five with normal parents, who had enlarged liver and spleen, were very similar in appearance and skin coloration but had no jaundice nor definite Gaucher's disease. The mother had five normal children by a previous marriage. Hartston (1931) reported a boy, his brother and a stillborn child of the same mother with enlarged liver and spleen.

Hand-Schüller-Christian Disease and Xanthomatosis

This syndrome was first reported by Hand in 1893, a three-year-old boy having diabetes insipidus, exophthalmos, a skin eruption, bronzed skin, enlarged liver and spleen. Postmortem examination showed yellow nodules in the skull and liver. Török (1893) observed hereditary xanthomatosis in several families. Schüller in 1915 made the first X-ray studies of a boy and a girl, but mistook the condition for dyspituitarism. Christian in 1919 agreed with him in diagnosing the case of a girl of five. Hand later studied a boy of seven. It now appears that the disease is closely related to xanthomatosis, both showing a derangement of cholesterin metabolism. The conditions are contrasted by Reich (1934). Xanthomatosis was regarded as the general condition of granulomatous infiltration of the bones and is found not only in children but frequently in adults from twenty-one to sixty-nine years of age. It is a disturbance of the stability of the emulsion of cholesterin and fat in the blood, but there is no hypercholesterinemia (excess of cholesterin in the blood). Landoff (1940) has made an extended study of the disease. The Hand-Schüller-Christian syndrome is now confined to those cases of xanthomatosis which also show defects in the skull and dyspituitarism, the fundamental change in both being a deranged cholesterol metabolism with yellow deposits in the skin and tissues. By 1935 there were sixty known cases of the Hand-Schüller-Christian syndrome.

Pick (1933) contrasted the hyaline storage cells of Gaucher's disease with the "foam cells" of Hand-Schüller-Christian disease and Niemann-Pick disease and pointed out many other differences in these syndromes. Horsfall and Smith (1935) also deal with the physiology. Jones (1939) describes a pair of MZ girl twins three years of age, one of whom developed symptoms of Hand-Schüller-Christian disease. There were bone lesions in the skull and humerus, but neither diabetes insipidus nor exophthalmos were present, the characteristic foamy cells were not seen nor was the blood cholesterol increased. The second twin, living under the same conditions, had not developed the disease a year later, but some doubt is attached to the diagnosis.

This disease occurs predominantly in Jews and, unlike Gaucher's disease, is found mainly in males. There appears to be no doubt about the origin of the syndrome through recessive inheritance. Rowland (1928) described two cases under the name *xanthomatosis.* Hilton and Eden (1941) do not distinguish it from the Schüller-Christian syndrome but describe the skeletal changes in an adult woman (the condition usually occurring in children, probably as a recessive). Thannhauser (1929) made an extensive comparison of all the lipidoses and described a Jewish family with *xanthoma tuberosum et plenum* and tendon xanthoma, which were interchangeable (Fig. 196). The essential inherited condition of xanthoma tuberosum, which causes the skin lesions, appears to be an excess of fats in the blood. In a *forme fruste* of xanthomatosis there were no yellow patches on the skin, but a high cholesterol content in the serum and carotenemia (carotin in the blood). Nine cases (4♂ 5♀) are reported in a family in three generations, inheritance dominant. Xanthoma or cholesterosis cutis was described by Fasold (1924) in 15 families, with 58 normal : 53 affected sibs. These pedigrees showed dominance for the most part, but frequently a generation (in one case two generations) is skipped. More recently xanthomatosis is found to be frequently associated with coronary thrombosis. See Engelberg and Newman (1943).

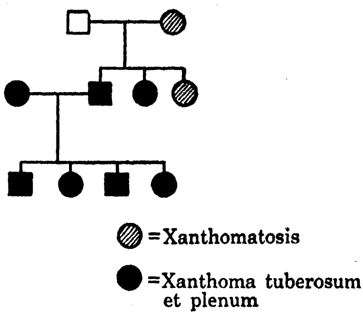

Fig. 196. Jewish family with xanthoma tuberosum et plenum and xanthomatosis. (After Thannhauser)

Xanthoma tuberosum is a rare syndrome in which nodules, tumors and plaques appear on the elbows, knees, buttocks and heels. The cholesterol content of the blood is also increased, but hypercholesterinemia may be present in individuals who are otherwise normal transmitters. Wilkie showed the condition to be hereditary in 1868. It is an incomplete dominant, frequently skipping a generation.

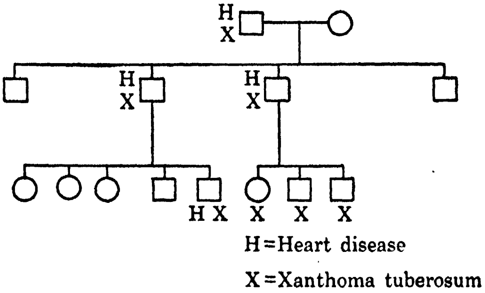

Fig. 197. Pedigree of angina and xanthoma tuberosum. (After Müller)

Müller (1939) describes lipoid deposits (xanthoma tuberosum) producing a special form of arteriosclerosis and "hereditary heart disease" in Norway. He found the condition inherited as a dominant in seventeen families, one of which is shown in Fig. 197. Fibrous pads which develop over the finger joints and are known as *Garrod's pads,* are inherited. In xanthoma tuberosum, nodes develop on the fingers and knees (Fig. 198), elbows, heels, and xanthelasma or yellowish plaques in the eyelids. Snapper and Parisel (1933) described a case of generalized xanthomatosis with accumulation of lipoids in the bones, but without the symptoms of Schüller-Christian's disease. The osteoporotic lesions of the bones were distinct from those of osteitis fibrosa generalisata.

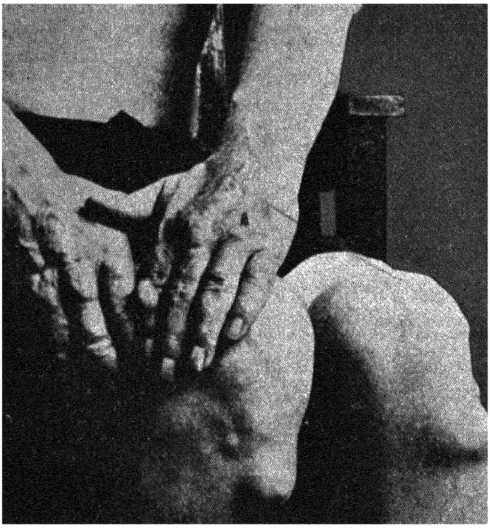

Fig. 198. Xanthoma tuberosum with nodes on fingers and knees. (After Müller)

Blood, Kaufman and Stevens (1942) describe a Syrian family in Philadelphia in which normal parents had five affected children in a family of nine, besides three which died shortly after birth and one which is still an infant. The syndrome develops at three or four years and the most serious effect is the cardiovascular disease, of which four died. Another child at eight years had high blood cholesterol and cardiac lesion but no skin effect, and another at four and a half years had hypercholesteremia, as had the father. One child dropped dead at twenty-three after walking to church. The heart showed coronary sclerosis and myocardial degeneration, and there were orange-yellow deposits in the arteries. A sister died of heart lesions at fourteen, another at six and a half and a brother at eighteen. It is probable that the hypercholesteremia is invariably present as a strictly dominant inheritance, the other features of the syndrome being more or less irregular in their appearance.

Thannhauser (1941) has recently characterised the various diseases involving lipoidosis as follows: Xanthomatosis without hyperlipaemia (excess of lipoids in the blood) is a hereditary disorder of metabolism of the reticulo-endothelial cells and histocytes, which increases the cholesterol in the cells. In xanthelasma there is excess of cholesterol in the blood. In the Schüller-Christian syndrome, with osseous deposits, the cholesterol in the blood is normal. Gaucher's disease, which is chronic in adults but acute in infants, is restricted to the lympho-haemopoietic system. In Niemann-Pick disease the histiocytes and reticulocytes in every organ may accumulate a phosphorized lipoid (sphingomyelin) causing rapid death. Lipoid nephrosis is distinguished by the absence of xanthomatosis of the skin. In von Gierke's disease (glycogen storage) there is also lipoid accumulation in the liver, kidneys and serum.

Niemann-Pick's Disease

Niemann described this disease in 1914 in a girl of seventeen month whose parents were Polish Jews. He distinguished it from Gaucher's disease by the early onset and rapid malignant course. Autopsy showed the spleen to be greatly enlarged with yellowish-white nodules, the liver and lymph nodes also containing lipoid materials. Pick (1933) contrasts this disease with the other lipoidal syndromes. It appears to be rarer than Gaucher's disease, fifteen cases having been reported up to 1933, and has even more predilection for the Jewish race. The foam cells, which can be found in all parts of the body, can be stained with lipoid stains, but they also show a great increase in phosphatids and an absence of kerasin. These cellular changes are found to be identical with those in Tay-Sachs disease (amaurotic idiocy), showing that both involve the same type of metabolic derangement, the effects of which are mainly confined to the brain and retina in the latter disease. Some cases show both diseases.

There can be little doubt that Niemann-Pick disease, which is also congenital, is inherited in the same way, as a simple recessive gene. Merksamer and Kramer (1939) describe three cases in one family, two of which had a cherry-red spot in the macula. Maurer (1941) records four other cases (two of them sibs), while Rothstein and Welt (1941) consider further the relation to infantile amaurotic idiocy. Niemann-Pick's and Gaucher's disease occur predominantly in females and Hand-Schüller-Christian disease chiefly in males. All three are accompanied by a yellowish-brown pigmentation of the skin.

Lipid proteinosis (Urbach-Wiethe disease) is recorded in single cases, generally from cousin marriages. The syndrome includes an eruption of yellowish plaques containing phospholipids, and mucous lesions of mouth and pharynx (see Ramos e Silva, 1943).

Progressive Lipodystrophy

This disease is included here although the change in fat metabolism, which removes all fat from certain portions of the body, is probably secondary to other inherited defects. The condition is rare except in Spain, where it seems to occur more frequently. It was first accurately described by Barraquer (1907) in a woman of twenty-five in Barcelona and later studied by Simons (1911–13), so it may be called the *Barraquer-Simons syndrome.* It is mainly found in women. Watson, Boog and Ritchie (1925) studied three cases and found over 50 cases described (17 ♂ 33 ♀). Many others have been recorded since. There is a progressive loss of fat from the face, neck, arms, thorax and abdomen, while abundance of fat is retained on the lower limbs. The result is like an ultra-Rubens below the mid-line and a skinny witch above. It may appear as early as at two years of age and some cases are fat as children. At the end of two to four years the lipodystrophy becomes stationary and is frequently followed by fat accumulation over the gluteal regions and the legs, the muscles remaining well developed. No explanation of this peculiar change in fat distribution (see Fig. 199) has been reached, although nervous and endocrine causes have been suggested, including basophilic hypopituitarism. An enlarged sella turcica was found in one case.

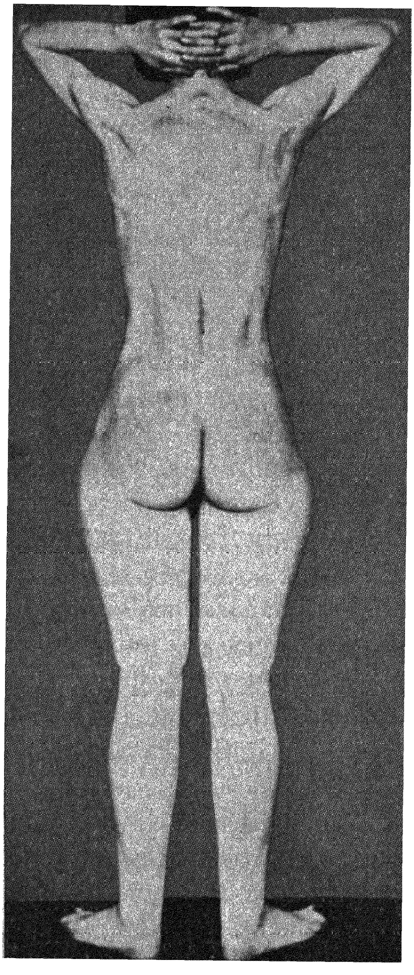

Fig. 199. Progressive lipodystrophy. (After Watson and Ritchie)

Marañon and Soler (1926) suggest cephalothoracic lipodystrophy as a more accurate name. They think it is due to hyperthyroidism and that its localization is based on neuro-vegetative factors. They find another type in which the fat accumulates in the upper part of the body. A case of loss of fat only from the lower legs is described by Bigler (1939) in an Italian girl twelve years old. A case in a boy of ten years was described by Cockayne (1931), the parents being normal and unrelated. Tallerman (1936) described a boy of ten with cephalothoracic lipodystrophy. The parents were unrelated, but the mother (presumably heterozygous) showed the condition in a minor degree. Barraquer-Ferré (1935) published the first familial case, a woman, her mother and maternal grandmother being similarly affected. In this case the disease appears to be dominant, whereas the many single cases described are presumably recessive.

Six cases in children were reported by Parmelee (1932), who reviews the literature. Van Leeuwen (1933) described a family in which lipodystrophy was combined with otosclerosis, bone cysts and mental deficiency. Three of seven sisters and four other relatives were affected.

Currier and Davis (1930) described the condition in a woman of sixty-five. Her brother, sister, half-brother and half-sister were obese from childhood and her mother's brothers and sisters all weighed over 200 lb. Of her five children, two sons weighed over 180 lb. In this family the disturbance in fat metabolism is associated with hereditary obesity. Smith (1930) describes the case of a woman in whom lipodystrophy appeared after the menopause. The loss of fat was in the lower half of the body, below the waist, the upper part being unaffected. Hartston (1933) found eighty-five cases of lipodystrophy recorded and describes the condition in two boys. He makes the erroneous statement that it is neither "hereditary, familial nor racial." The onset is usually in childhood, before eight, according to him, but it may occur from two to sixty-five years. The loss of fat occurs down to the umbilical level and it is more than twice as common in females as in males.

Lipoidosis of the skin and mucous membranes is an inherited condition in which small raised yellowish papules are present on the face and scalp, warts on the fingers and small bluish-violet tumors on the elbows. The mucous membrane of the lips, mouth, palate, pharynx and larynx is also studded with yellowish-white plaques. These lesions are present at birth, together with laryngeal tumors. A lipoid of the phosphatide group, which differs from the lipoid of multiple xanthomata, is infiltrated in the cutis. The condition is very like xanthoma tuberosum multiplex and is allied to Gaucher's and to Niemann-Pick's disease. Further details of this very rare disease are given by Cockayne (1933). It is a monogenic recessive in inheritance, the parents being normal but frequently related.

Dercum's disease (adiposis dolorosa) is a condition of *painful* obesity associated with asthenia and psychic disturbances. Dercum (1892) described three cases in women who came respectively from Ireland, England and Germany. Winkelman and Eckel (1925) reported two hundred cases in the literature and described an obese negress with enlarged sella turcica. It is regarded as pluriglandular in origin and Keusch (1936) records two heredofamilial cases. The condition is five times as frequent in women as in men but the manner of inheritance requires elucidation.

Gout

In former centuries, when gout was much more frequent than now, its occurrence in successive generations of a family was often recognized. Dr. Johnson remarked in 1773 that Dr. Cadogan's contemporary book on the gout was foolish in maintaining that gout is not hereditary. In modern times little attention has been paid to the inheritance element. According to Macklin (1934), Osler states that 50 to 60 per cent of gout patients have a family history of the disease, its occurrence more frequent in men than women. In gout, large amounts of uric acid and sodium biurate may be deposited in the joints. Other mammals than man and the chimpanzee have a uric acid oxidase in their liver, which converts uric acid into the harmless water-soluble allantoin. The absence of this enzyme in man makes gout possible. However, it has been shown that Dalmatian dogs have the enzyme uricase in their liver although they, unlike other carnivores, excrete uric acid (Trimble and Keeler, 1938). This condition is shown to be a simple recessive in crosses, and the harlequin spotting of Dalmatians is determined by two genes in another pair of chromosomes. In humans, uric acid is derived via xanthine from nucleic acid, the xanthine being formed from the two purine bases, adenine and guanine, in nucleic acid.

Llewellyn (1922) records estimates of an ancestral taint in 75 to 81 per cent of private patients in England. He regards it as "purely hereditary," the pathological groundwork being a tendency to cellular sensitization (latent gout), i.e., it is in part allergic in origin. Like asthma, it is paroxysmal and periodic, the disease being precipitated when the sensitized cells encounter the appropriate protein or other allergen. Poisoning of the vascular endothelium would result. The deranged uric acid metabolism is an independent but associated condition. In a more recent study, Talbott (1940) found high serum urate in 25 per cent of 136 relatives of 27 gout patients without any symptoms. The localization of allergic arthritis has been shown by means of urate administration. Smyth and Freyberg (1940) made a hereditary study of two gouty families. It may be suggested that the factor determining high serum urate and the allergic factor are distinct but genetically linked in the production of gouty arthritis. Whether linkage is involved can only be determined by the study of families. In any case a disturbed purine metabolism appears to be involved in arthritic gout.

In a study of thirty families, not yet completed, Stecher and Hersh (1945) regard it as primarily a metabolic disease with hyperuricemia, penetrance being incomplete and a second factor involved. They find that 3.7 per cent of whites show hyperuricemia, this condition occurring also in leukemia, acute hemorrhage and kidney insufficiency.

Diabetes Mellitus

A chronic disturbance of the metabolism, manifesting itself especially by increase in blood sugar (hyperglycaemia) and by excretion of sugar in the urine (glycosuria). It causes emaciation, loss of strength, thirst, and polyuria and finally diabetic coma. A diabetic patient's life may be maintained indefinitely by giving insulin, the condition being primarily due to a deficiency of this secretion from the pancreas.

Thomas Willis described diabetes in 1674, although it had been recognized much earlier. He discovered the sweet taste of the urine in certain cases and so established the basis for distinguishing d. mellitus from d. insipidus. Erasmus Darwin in 1778 further distinguished the two types, but the problem of their relation remains to this day. The very complicated physiology of diabetes has been discussed in different aspects by Young (1941) and Soskin (1941). Diabetes may result from primary changes in the islets of Langerhans in the pancreas (which normally produce the hormone insulin), but in many cases it is preceded by increase of weight resulting from pancreatic-pituitary imbalance.

Anterior pituitary extract is shown to have a diabetogenic action in animals, producing increased growth in pups together with polyuria and glycosuria. The pituitary also produces a rise in islet tissue and insulin content of the rat pancreas. Adult dogs can be made permanently diabetic (with atrophy of the islets) by a short treatment with anterior pituitary, the same extract producing increase in weight or diabetes according to the age of the dog. The increased function of the islets associated with the increase in weight neutralizes the diabetogenic influence of the anterior pituitary. But the increased pituitary functioning is temporary and may be followed by diabetes. That intravenous injection of alloxantin will produce diabetes in rabbits is shown by Koref, Vargas, Rodriguez and Telchi (1944). Histological study shows that this substance has a selective affinity for the cells of the islets of Langerhans. Defective metabolism of alloxan or of purines may therefore play a part in the etiology of diabetes.

Sugar is formed by the liver, both from protein and from fatty acids, and it also arises from food in the alimentary canal. A rise in blood sugar (hyperglycaemia) may result from an increased supply, a decreased utilization, or both. Thyroxin from the thyroid also increases the blood sugar, and in diabetes there appears to be secondary atrophy of the thyroid. Adrenalectomy lowers the blood sugar and other carbohydrate stores in the body, the adrenals probably affecting carbohydrate metabolism both directly and indirectly. In diabetes, the liver wastes the protein and fat of the body by pouring excess sugar into the blood, whence it is lost in the urine, thus causing loss of weight in the individual. This is followed by ketone formation, with ketonemia and ketonuria. Lack of insulin causes the final coma. Insulin is important in the endocrine balance which determines the normal blood sugar level. It is a protein which has been crystallized and contains zinc in the molecule. Diabetes mellitus is then not necessarily or usually due to a pathological pancreas. The syndrome of symptoms may also include pituitary diabetes and, less probably, thyroid or adreno-cortical diabetes. Certain cases may arise from hepatic damage. As the possible causes of diabetic symptoms are so diverse, it is clear that the hereditary bases may be equally diverse in different families.

An infection may result in pancreatic sclerosis, causing inadequacy of the islet tissue; but this condition will not be inherited. Cammidge and Howard (1930) have shown that in mice both hyperglycaemia and hypoglycaemia are inherited as simple recessive conditions. Formerly human diabetes was frequently regarded as dominant, but later work, especially of Pincus and White (1933, 1934), in which statistical corrections are applied to the data, gave results closely in accord with a simple recessive.

In one hundred cases of acromegaly (which is produced by hyperpituitarism), twenty-five had glycosuria, and twelve of these were true diabetics. If the pituitary tumor associated with acromegaly is removed, the diabetes may disappear, so there is no permanent lesion of the pancreas. Coggeshall and Root (1940) studied twenty-nine cases of acromegaly with diabetes. In six of them hereditary diabetes was present in the family. That both conditions result from the same pituitary derangement seems more likely than that they are due to two linked genes. It is known (Hinsworth, 1936) that there are two types of diabetes in relation to insulin: (1) insulin-sensitive, caused by a deficiency in insulin, (2) insulin-insensitive, due to lack of an unknown factor. Type 1 easily develops hypoglycaemic symptoms. These types may be genetically distinct. Hinsworth (1939) regards the essential lesion in diabetes as a diminished ability of the tissues to utilize glucose, and hyperglycaemia as an attempt of the body to compensate for this.

A condition called *skin diabetes*, characterised by dermatitis, farunculosis or pruritis, with sugar accumulated in the skin but no hyperglycemia, is designated by Urbach (1945). It frequently occurs in obese individuals with a purplish red complexion. Whether there is any connection with pancreatic diabetes remains uncertain.

Diabetes is uncommon among the Chinese, in whom it is mild and accompanied by supersensitiveness to insulin. The symptoms are mild also in Japan and India except among the wealthy classes. Mills (1930) finds that the incidence is low in Ireland, but higher among the Irish in Boston. He concludes that the incidence is largely affected by climatic conditions. In the United States it is lowest in the southern states, then in the western mountain states, then in the northern and middle states, highest in the northeastern states. This is not explicable on racial grounds. The death-rate of Negroes from diabetes is higher the farther they are removed from their natural tropical environment, but in general it is lower than in whites. In Europe (except Ireland) all countries north of the 50th parallel have a diabetic death-rate above 9.6 per 100,000, all below it have a lower rate. No relation to sugar consumption was found. The death-rate per 100,000 ranges from 30 in Japan to 15 in England, 4 in Finland and 25 in New York. Its higher incidence in the Mediterranean region is probably racial in origin. The curve has risen steadily in all countries since 1880 (except during the war of 1914–18) and diabetic mortality is estimated to have increased in a century from 1 to 20 per 100,000. The world's sugar consumption has also increased twentyfold during this period. It has recently been found that diabetics have a much higher cancer incidence than the general population. For recent statistics of the frequency of diabetes mellitus in United States army testees, see Spellberg and Leff (1945). These results again show a low incidence in the South (only 0.28 per 1000, among 32033 in New Orleans) and a high incidence in New England (4.5 per 1000, among 45650).

Finke (1930) found a familial frequency of 25 per cent for diabetics, which he regards as indicating that it is a simple Mendelian recessive. He describes a family with 15 cases (5♂ 10♀) in four generations, strictly dominant. He considers that sporadic cases are also inherited (recessive) but found no evidence that diabetes in children is hereditary. A correlation between diabetes and obesity is certain, but it is uncertain whether gout and arteriosclerosis are commoner in diabetics than in non-diabetics. Hanhart (1939) studied 91 cases (43♂ 48♀) of diabetes in children under twenty in the child clinics of Zürich and Basel.

Of these, seventy-nine were probands. He found the inheritance a simple recessive with 100 per cent penetrance. He recognizes that dominant forms also exist. We may conclude that *diabetes mellitus follows the usual law, the recessive form being severe with early onset, the dominant form having at least a later age of onset and generally milder symptoms.* Occasionally, the recessive form appears in successive generations when one parent is homozygous and the other heterozygous for the gene.

Levit and Pessikova (1934) collected 258 pedigrees in Russia. They found 20.7 per cent of the cases to be familial. Healthy near relatives of diabetics were tested and four out of forty were found to have abnormal curves of blood sugar. The symptoms were found to be very variable, even in the same family, but apparently one dominant gene was involved. The reduced fertility of patients would explain the "anticipation." In a study of families and twins, Steiner (1936a) finds 35.1 per cent of cases familial. The corrected expectation of diabetes in the parents of probands was 4.1 per cent, in sibs 19.8 per cent and in children 16.6 per cent. When both parents were diabetic, one-quarter to one-third of the children were affected.

Joslin (1940) points out that before the introduction of insulin in 1922, 80 per cent of adult diabetics were markedly overweight. Insulin therapy led to the survival of diabetic children, only 2 per cent of whom were overweight. Recessive Mendelian ratios were found in a large series of cases selected at random. Inheritance was also shown by studies of 19 MZ and 29 DZ twins found among 17,000 diabetic cases; in 63 per cent of the former but only 7 per cent of the latter pairs both twins were diabetic. Similarly, Berg (1939), in a study of 46 identical and 87 fraternal twins, found that in 65 per cent of the former and 22 per cent of the latter both had diabetes. The higher incidence in Jews is confirmed, but there is no relation to blood group. Pincus and White (1934), who have also made extensive clinical and statistical studies of diabetics, find that many apparently normal relatives of diabetics are in fact potential diabetics. They emphasize the importance of age incidence, showing that diabetes may appear even as late as the ninth decade, and failure of the islets to function they regard as premature senility of the pancreas. They determined the blood sugar concentration and gave glucose and sucrose tolerance tests to 169 close relatives of diabetic patients. Hyperglycaemic individuals were found in diabetic families. About 14 per cent of the relatives of diabetics given blood sugar examinations and 25 per cent of those given sugar tolerance tests had abnormally high blood sugar values and are believed to be future diabetics (genetic formula **mm**).

No test for **Mm** persons has yet been devised (**MM** being normal homozygotes).

It is clear, however, that all types of diabetes do not conform to this recessive inheritance. Cammidge (1928) published three clearly recessive pedigrees, two clearly dominant (see Fig. 200) and one (Fig. 201) which is probably an irregular (conditioned) dominant. If this were recessive, II. 4, III. 2 and IV. 4 would all have to be heterozygous. Wright (1931) has also published several dominant pedigrees with a total of 16♂ and 25♀ affected. Cammidge (1934) finds the dominant form nearly always mild and easily controlled by diet alone, persisting for many years without affecting the general health, whereas the recessive form is generally grave from the onset and requires insulin therapy. The danger of statistical methods is that they lump together dominant and recessive pedigrees. The evidence seems clear that both occur in diabetes mellitus, although the latter are more frequent. Statistically they should have separate treatment.

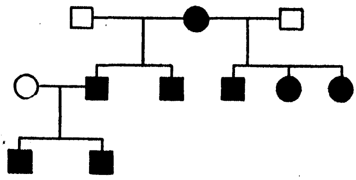

Fig. 200. Dominant pedigree of diabetes mellitus. (After Cammidge)

Steiniger (1939) also finds that diabetes is dominant in some families and recessive in others. There is not 100 per cent penetrance of the gene, but environment also plays a deciding part. Many will die of other diseases before they reach the diabetic age. The gene milieu or constitution may also have a strengthening or weakening effect on the expressivity and penetrance of the diabetic gene. Accidents, sepsis and other conditions may affect the function of the islets. Extra-insular diabetes may be of renal or pituitary origin or may arise from a derangement of the cerebellum. The tendency to these secondary forms of diabetes may also be inherited, so that various biotypes, not necessarily alleles, may exist. Anticipation is found to occur in about three-fourths of the pedigrees and post-dating in about one-fourth. The former is explained by the accumulation of subgenes favoring diabetes, according to the theory of Goldschmidt (1938). The reproduction of diabetics is shown to be much reduced. No woman reproduces after the symp-

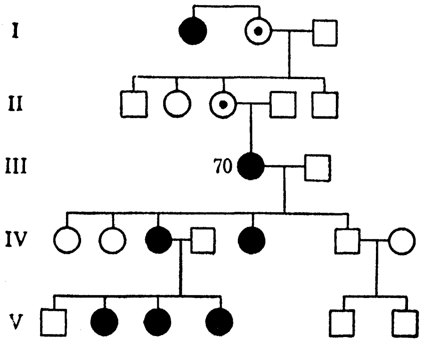

Fig. 201. Diabetes mellitus inherited as a conditional dominant. (After Cammidge)

toms of diabetes develop. Twin studies of Then Bergh are quoted, showing concordance in the year of onset after the forty-third year, but discordance even in MZ twins at earlier ages owing to environmental effects. Lemser (1938) studied forty-nine pairs of diabetic twins and shows that not every bearer of the factors for diabetes will develop the symptoms (Table 16).

TABLE 16

DIABETIC TWINS

	Number	*Concordant*	*Discordant*	*Undetermined*
1-egg	19	15	3	1
2-egg and different sexed	30	6	23	1

A characteristic pedigree (Kennedy, 1931, Fig. 202) shows 10 cases (5♂ 5♀) in two generations. Five of the eight cases in generation III had amputations for diabetic gangrene. All were overweight and I. 2 probably died of diabetes. The large excess of normals in sibships indicates low penetrance. Allen and Mitchell (1920) studied a diabetic family of "poor whites" in South Carolina with nine cases in three generations. The father of the third generation was a blue-eyed brunet, the mother a blond. Of their thirteen children, six were diabetic. Four of the diabetics had blue eyes and dark hair like their father, while the five who had the eye and hair color of their mother were free from symptoms. Landis (1921) reports the converse relationship, a diabetic family in which the disease was present in the five blond, absent in the four brunet children. This indicates that the gene for diabetes is in the same chromosome as those for eye and hair color. Barach (1926) also finds diabetes associated with fair hair and light complexion, as well as obesity and short stature.

Cowen (1936) made a study of fifty-four diabetics in Zürich. They were generally over fifty and only one was a child — a girl of fourteen. Where diabetes occurred in the ascendants it was found to be an irregular dominant with low penetrance in six families and probably recessive in three. About thirty-seven were of more or less pycnic constitution. Besides the hereditary factor, environmental influence affects the time of onset, so that early recognition and treatment of the condition is very important. Draper *et al.* (1940), using Sheldon's constitutional technique, distinguish between the pancreatic and the pituitary forms of diabetes, the former being thin, the latter fat. The obese were afterward divided into two subgroups, (*a*) more muscular, (*b*) becoming obese. In this way 225 diabetics were classified; group 1 were insulin sensitive, with an acute onset and severe symptoms. In group 2 the onset was insidious, the conditions more stable and with less response to insulin. The clinical and morphological grouping corresponded in 88 per cent of cases.

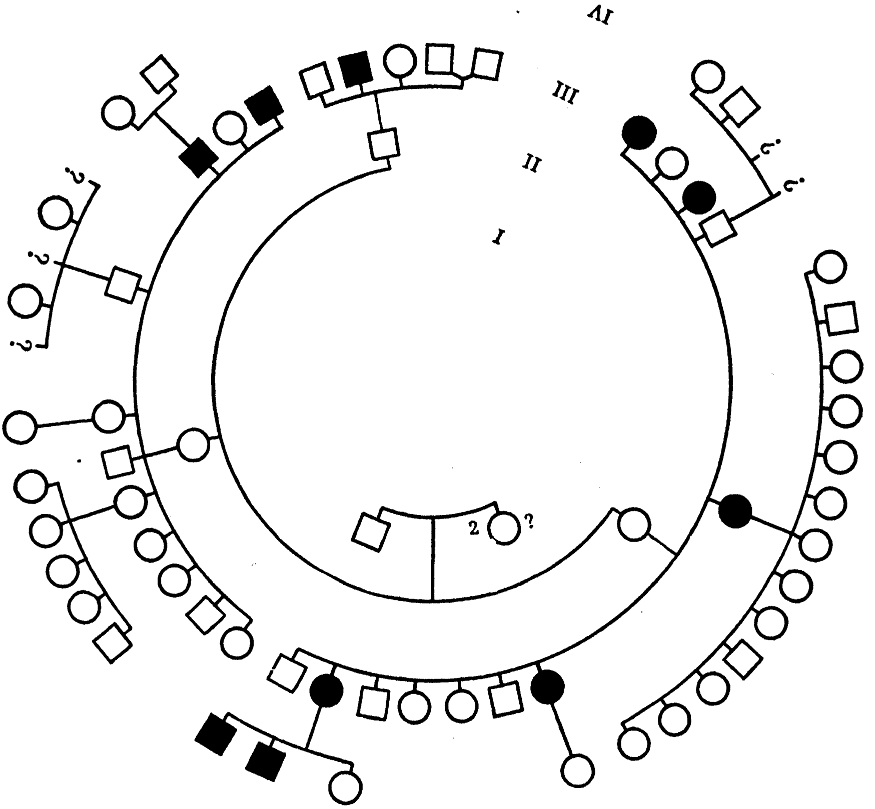

Fig. 202. Pedigree of diabetes mellitus. (After Kennedy)

The death-rate from diabetes has continued to increase notwithstanding the use of insulin. As diabetic women at least seldom reproduce, the racial dysgenic effect of insulin therapy in multiplying diabetics by heredity may not be great. Gibson and Fowler (1936) report 8 cases (4 boys 4 girls) sixteen to twenty years old, with severe diabetes and signs of infantilism and dwarfism which are attributed to hypofunction of the anterior pituitary. This is not in accord with recent work on the interrelations of the pituitary and the pancreatic islets.

Cole, Harned and Keeler (1941) obtained a strain of rats with low-glucose tolerance (the usual precursor of diabetes), obesity and related symptoms, hyperactivity of the pituitary being postulated as the basic cause. When this diabetic strain was crossed with a non-diabetic strain, the F_1 showed less glucose tolerance than either parent. In F_2 there were no females and few males with low tolerance, a few showing higher tolerance than either original strain. The results are interpreted in terms of a principal gene with modifiers, the principal gene tending to be incompletely recessive, and its penetrance is less than 100 per cent even in the homozygous condition. These results may be directly comparable with those in man.

Hyperglycaemia has been described as a recessive Mendelian character in mice (Cammidge and Howard, 1926). The sugar content of the blood in a strain of mice was found to vary. Breeding experiments showed that high sugar content (about 120 mg.) is recessive to normal (about 80 mg.). When a heterozygous normal is bred to a mouse with high sugar content, the offspring show equal numbers of the two types. This condition was independent of coat color.

Orthoglycaemic glycosuria, or "leaky kidneys," with sugar in the urine but no rise in blood sugar, is a benign condition which does not progress to diabetes mellitus. Hjärne (1927) investigated a family in Sweden and Finland having this condition. Six generations were descended from a single pair, the last three generations being examined. Among 199 persons, 18 (in perfect health) had orthoglycaemic glycosuria, 19 had glycosuria without diabetic symptoms, 7 had diabetes mellitus, and 2 others were aberrant. Normal parents without glycosuria had in 13 cases only normal children (44). Orthoglycaemic glycosuria was present in younger persons of both sexes and was inherited as a monofactorial dominant. The diabetes in the pedigree was an independent unrelated condition. When the father had orthoglycaemic glycosuria and the mother was diabetic there was no summation of effects in the children. Holst (1926) describes eight families in which both diabetes mellitus and glycosuria occurred. These cases of glycosuria were of no definite type, but included cases due to alimentary hyperglycaemia as well as the renal form. He concludes that there must be a hereditary relation between diabetes and the non-diabetic glycosuria. The nature of this relationship is uncertain. Hatlehol (1924) made an extensive study of blood sugar in twelve families with *benign glycosuria*, in five of which diabetes was present. He studied especially the threshold values in diabetes and in benign (renal) glycosuria, which remain relatively constant. He thought the condition due to a metabolic disorder rather than a renal abnormality.

It is not without interest that Eyster (1924) found a type of maize with yellow seedlings which were unable to use the glucose formed from the carbohydrates in the endosperm. Glucose dripped from the leaf tips and the seedling soon died. To this extent the condition is like glycosuria. It was inherited as a simple recessive.

Bowcock (1929) described a family with 18 cases (7♂ 11♀) of glycosuria in four generations. It was a dominant with one skip, and one case developed into diabetes mellitus.

Parkes Weber (1931) described another family with normal blood sugar but sugar in the urine. A woman of fifty-seven had passed sugar

(1 to 4 per cent) for at least forty-four years, but without hyperglycaemia, polyuria, excessive thirst or other signs of diabetes. Her parents were first cousins and she had three normal sibs. Of her five children, four by the second marriage were all affected. This non-symptomatic condition is probably an irregular dominant. Marble (1932) found only 15 cases (8♂ 7♀) of *renal glycosuria* in a critical analysis of 9000 consecutive cases of glycosuria. The inheritance of this rare condition may be recessive or possibly an irregular dominant.

Rhind and Wilson (1941) report a family having diabetes mellitus with Addison's disease. Only fourteen cases have been recorded, five of them doubtful. In this family the father and five children were afflicted and four of them died at an early age. Another daughter has glycosuria of pregnancy and a son died of phthisis.

A striking case of multiple defects having evidently a genetic basis is cited by Tyrer (1943). A boy of eighteen was undersized, with a small pituitary, hypogenitalism, bilateral inguinal hernia, diabetes mellitus, marked mental retardation, optic atrophy, left macula degeneration and goitre. There were evidently defects in the pituitary, sex, pancreatic and thyroid glands. His mother's two sisters also had goitre, but the family lived in a region of endemic goitre. The boy's parents were cousins, the father's brother had epilepsy and the paternal grandmother was psychotic. The boy had one normal sister, another sister had epilepsy, diabetes and optic atrophy. A brother five years old already had epilepsy and diabetes. In this family there were strong indications against cousin marriage.

Unlike diabetes mellitus, *diabetes insipidus* is clearly a simple dominant and relatively rare in its occurrence. Weil's (1884) classic case of *diabetes insipidus*, or polyuria, with 23 affected (14♂ 9♀) in four generations, is shown in pedigree form in Fig. 203. In eight sibships

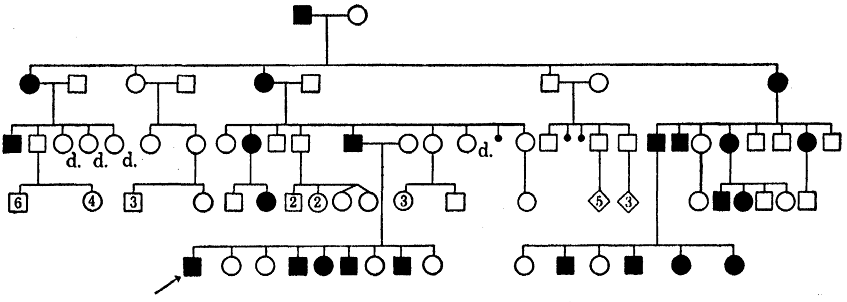

Fig. 203. Pedigree of diabetes insipidus. (After Weil)

from DR × RR there were 22 affected to 22 normal and four who died young. In this disease the patient develops excessive thirst and drinks large quantities of water, but may live to old age. Some of these persons drank 6–8 litres of water daily. The condition may be either congenital and inherited or acquired and non-inherited — i.e., it may result from an inherited germinal change or from an impressed modification (phenocopy). In Weil's case, also cited by Bulloch (1909), the original progenitor was born in 1772 in Oberhessen and had 220 descendants in five generations, 34 of whom had diabetes insipidus. Weil, Jr. (1908) added eleven cases in the fifth generation of this family, making 34 cases (22 ♂ 12 ♀) in five generations, the sibships numbering 34 affected: 46 normal. This is an ordinary dominant pedigree except for the excess of normals and one skip of a generation. Camerer (1935) added to Weil's pedigree two cases in the sixth generation, the total numbers of affected to normal being 35 : 33. The family is now widely scattered in Germany and America. Chase (1927) gives another pedigree in five generations showing inheritance as a Mendelian dominant. One man in this family would drink a pail of water without taking it from his lips. He lived to eighty-five years of age. Marañon and Bonilla (1925) describe the condition in mother and son. The latter, when only twenty months old, drank about eight litres of water per day.

Allan and Rowntree (1931) discuss the relation of the two forms of diabetes. In certain cases d. insipidus develops into glycosuria and d. mellitus. These authors describe two cases in which both forms are present in the same person and one in which transitory glycosuria preceded d. insipidus. The cases of association are very few and appear to be simply coincidences. The gene for one is always dominant and, for the other, generally recessive. It is suggested that the same intracranial lesion may be responsible for both polyuria and glycosuria, but this is unlikely. The use of pituitary extract for control of the former does not interfere with the effectiveness of insulin in controlling the latter. Of course d. insipidus is rare in comparison with d. mellitus, although, being dominant, many more affected individuals may occur in a family pedigree. The two main theories of its etiology are (1) endocrine, (2) nervous. Lindeboom (1933) explains the case of another patient with both types of diabetes.

Gänslen and Fritz (1924) described a family with 19 cases (10 ♂ 9 ♀) in five generations, all descended through two previous generations from a couple who married in 1680. After the two generations whose condition is uncertain, there is no skip, the sibships numbering 19 affected : 21 normal. The proband drank 10 to 12 litres of fluid daily and as a prisoner of the French in 1918 slaked his thirst with anything from urine to rainwater without harmful effect. This condition is a family tradition but their overpowering thirst does not lead to alcoholism. The craving for alcohol is not thirst. Blotner (1942) described a family with son, mother and grandmother affected.

Eaves (1930) found 14 cases in 100,000 patients. Levit and Pessikova (1936) collected sixteen pedigrees in Russia, only three of which were familial and these having only two or three cases, the rest being single cases. Unlike the few large pedigrees hitherto published, they find diabetes insipidus to be a conditioned dominant with very low penetrance, accounting for the large number of sporadic cases in this way and not as mutations. They emphasize the necessity to collect all cases of any abnormality and not merely the striking ones. Even the large pedigrees show occasional skips, but it is clear that they really have a higher penetrance than the families with few cases.

Richter (1930) showed that a fine puncture in the brain-stem of a rat near the pituitary will produce permanent diabetes insipidus (polydipsia and polyuria). One rat drank nearly twice its body-weight of water each day. This leaves little doubt that the pituitary theory of human d. insipidus is correct. Pasqualini and Avogadro (1942) show in two human subjects that the injection of five units of the pressor hormone of the post-pituitary causes the complete loss of thirst in twenty minutes. The secretion of this hormone is controlled by nerves from the supraoptic nuclei of the brain.

Davidenkov (1940) describes the extraordinary condition he calls *aglycophagia*. The anomaly was observed in six members of a family pedigree, including two groups of cousins with no inter-marriages. In one family of seven, two are unable to eat sugar. The other family has four of five children effected, one to a milder degree. The parents and grandparents have no food idiosyncrasies. The affected members are sound, but a few have headaches and general nervousness. B cried when, as a child, he was made to taste a sweet bun. He cannot eat sugar, honey, jam, cakes, candies, chocolates, ice-cream or fruits or berries, except cranberries and bilberries. He cannot use saccharine. He likes a sweet taste, but sweet food brings nausea and physical weakness. When given sugar he became feverish, complained of pain in the stomach, and his pulse was affected. His cousin F disliked sweet things.

Since they cannot take saccharine, their reaction cannot be a chemical effect of carbohydrate, especially as they can eat starch, which is converted into sugar. It must then be the sweet *taste* which incites the pathological condition. It can hardly be an allergy, nor is it a metabolic derangement. It is regarded as nearest to myoplegia because of the difficulty in swallowing. The inheritance is apparently recessive.

The hereditary element in *obesity* is difficult to analyze in some cases. Gurney (1936) made a study of sixty-three stout women in Buffalo. Each was over 15 lb. heavier than the average for her age and height. When both parents were stout, 73 per cent of the children were stout. Stout × non-stout gave 170 offspring, 41 per cent stout. Non-stout × non-stout had 176 children, of whom only 9 per cent were stout. There is no statement regarding the age of the offspring.

There is evidence that obesity may be produced by dystrophy of the thyroid or of the pituitary and there may also be a type of obesity due to a factor affecting the cell metabolism. (See also Chap. XVIII.) *Lipomatosis* is the name applied to a local accumulation of fat, but there is no sharp line between this condition and general obesity. Bauer (1922) classified fat types of women as (1) the Rubens or girdle type with fat around the abdomen and buttocks. This accounts for 90 per cent of fat women. (2) The trochanteric type with fat in the upper thighs. (3) Fat from hips to knees or ankles (piano-leg type). (4) Sometimes excess fat limited to calves or ankles. (5) Excess on back, upper arms, breasts, neck and face. Excess fat on the buttocks and breasts is a racial characteristic of the female Bushmen and is known to be of prehistoric occurrence in Europe. The localization of fat in the other types is also probably inherited, but with more variation.

Lipophilia or avidity to store fat is then characteristic of particular tissues. It has been found that when, following a burn, skin from the abdomen is grafted on the back of the hand, it will store fat so as to require an operation for fat removal many years later. Individuals thus differ in their lipophilic tissues and obesity is constitutional in the vast majority of cases. Bauer (1941) analyzed 275 cases of obesity and found that in 73 per cent one or both parents were obese. Increased appetite, leading to fat storage, is considered to be the result of abnormal inheritance. It in turn appears to involve endocrine and nervous differences. There is also said to be a type of obesity which results from a highly efficient digestive system and a small appetite.

Ellis and Tallerman (1934) made a study of fifty cases of obesity in children. In thirteen cases the mother was grossly overweight, the father in six and both parents in three. The obese showed increased carbohydrate tolerance in the endogenous type, but not in the exogenous (non-inherited) group. Further analysis of obesity inheritance is needed. Heinbecker, White and Rolf (1944) conclude from the medical literature that lesions of the hypophysis, the hypothalamus or both may lead to obesity. This view is supported by many experiments with dogs. Various forms of inherited obesity may thus be expected to occur. For constitutional types of obesity see Bauer (1945).

Goitre

Goitre is endemic or sporadic. The enlarged thyroid is a pathological distension of the vesicles of the gland by a clear substance called *colloid*. The condition results from (*a*) an exogenous factor, lack of iodine in the soil water or in the food (marine fishes contain much iodine), (*b*) an endogenous factor, inefficiency of the thyroid in abstracting iodine from the food or its sensitiveness to lack of iodine. Endemic goitre occurs in regions where the normal thyroid cannot get enough iodine. Sporadic goitre results when the thyroid efficiency is far below the optimum. A sub-optimal environment will bring out any inherited deficiency in the thyroid, so the inheritance can be more easily studied in an endemic region where the cases are more numerous. Enlarged thyroids in dogs and even in brook trout can be cured by the use of iodine. Thyroxin was isolated from the thyroid in 1915. Recent work (see Harington, 1944) makes it very probable that this substance is formed in the body from tyrosine, with diiodotyrosine as an intermediate step. There is evidence that the first step of this transformation is controlled by an intracellular enzyme. The inheritance element in goitre may then be based on the lack of this enzyme. It is probable, however, that many hereditary factors exist which influence iodine utilization in the body.

Cabbage goitre can be caused by too much cabbage in the diet. A heat-stable substance produces thyroid hyperplasia in rabbits, but the cabbage also contains an antigoitrogenic substance (Marine *et al.*, 1930). It has recently been shown (Wilgus *et al.*, 1941) that soybeans will produce goitre in chicks and in young rats, but iodine will counteract the effect. The sulphanilamides and thiourea are also now known to cause enlargement of the thyroid.

Riddle (1929) established thyroid races of ring doves by selection, some having large and some small thyroids. Crosses between these strains apparently remained intermediate for three generations, but the analysis as regards factors and dominance was incomplete. Thyroid size was shown to be influenced by many external and internal conditions, including altitude, diet, season, state of nutrition, unsanitary surroundings, iodine intake, age, intestinal flora, other endocrines, disease, and by sexual and psychic states. As in man, a large thyroid may mean over- or under-functioning. McCarrison (1930) showed in Coonoor, South India, that when rats were fed on diets deficient in vitamins they developed goitre, with the usual excess of females affected. Giving iodine to such rats favored goitre-production. In this stock of rats the thyroid was about half the size of that in the American strain. In earlier work in India, McCarrison (1909) had studied the endemic *cretinism* in the Chitral and Gilgit valleys and concluded that defective thyroid function in the mother was the essential factor in the production of cretinism in the child, a "nervous" type of cretin being produced, due to the action of toxic agents on the thyroid of the child *in utero*.

In later experiments (McCarrison, 1914a), cretinous rats and goats were produced by giving the mother drinking water containing foecal matter from goitrous persons. This and other evidence led to the conclusion that cretinism and congenital goitre are both due to the action of toxic substances from the maternal intestine on the thyroid of the foetus. As only certain rats in a litter were cretinous, there is presumably here also an hereditary element. From a further study of the water supplies at Sanawar, in the foothills of the Himalayas (a region of endemic goitre), he concluded (1914b) that endemic goitre was not dependent on the geological structure of the soil but was produced by micro-organisms in the water supply. In regions of better sanitation, this factor should be of little if any effect. Eugster (1937) thinks endemic goitre is connected with the carbon dioxide content of the soil and hence with the nature of the carpet of vegetation.

Rüdin (1932) reviewed the various causes suggested for the endemism of goitre, especially in mountainous regions, and emphasized the possible effect of radioactivity of the rocks, but was unaware of the previous animal experiments. Zehnder (1937) made a study of seventy-eight Swiss cretins and from their physiognomy divided them into full, three-quarters and half cretins, also a small type without goitre. The cretinous types were fully characterised, with many anthropometric measurements.

Female animals have more iodine per unit of body weight than males. They are hence more susceptible to iodine shortage. Temporary physiological enlargement of the gland may take place in females at puberty or perhaps in cold weather. In New Zealand the iodine content of the soil water was shown to be correlated with the incidence of goitre, which occurs in both Europeans and Maoris.

Endemic goitre is well known in mountainous regions such as the Alps, Pyrenees, Andes and Himalayas. It was recognized in the Alps in Roman times by Juvenal and Pliny, and Marco Polo described the condition in the Central Asian plateau in the thirteenth century. It also occurs, for example, in parts of Germany, England and the United States.[2] Severe endemic goitre is accompanied by cretinism, i.e., congenital hypofunction of thyroid in the children, causing arrested physical and mental development and dystrophy (see Fig. 207, p. 561). A pedigree by Kutschera (cited by Pfaundler) shows nine cases of goitre and fourteen of cretinism in a Tyrol family (Fig. 204). Taussig (cited by Pfaundler) found that of 282 mothers of cretinous children, 95·7 per cent clearly had goitre. He concludes that there is no cretinism without a goitrous mother. The cretinous or cretinoid children were generally born in a consecutive series. When the wife was free from goitre at marriage they came in the middle of the sibs; when she already had goitre at marriage they came more at the beginning. The physiological and genetic relations of cretinism to goitre remain to be elucidated.

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[2] Pflüger (1937) has made a study of the geographical distribution of endemic goitre in Europe.

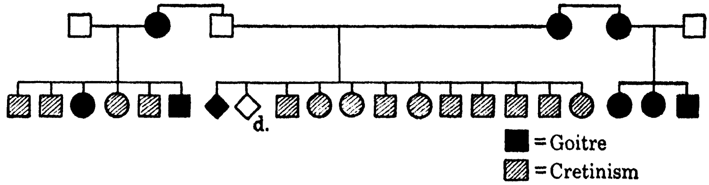

Fig. 204. Pedigree of goitre and cretinism. (After Kutschera)

A study of eighty-nine cases of cretinism (Lewis, 1937) in London of ages three to fifty-eight years showed that the mental improvement following thyroid treatment is seldom as satisfactory as the physical. In fourteen families there was one other member (parent or sib) who was dull or feebleminded without cretinism. In America an exaggerated form of hypothyroidism exists (Gordon, 1922) which should be called *myxoedema* in children. It is not uncommon (340 cases in the literature), is twice as frequent in females as males, shows both mental and physical retardation and is sometimes familial. Some cases are "curable" by thyroid, but the widespread character of this hereditary thyroid deficiency is insufficiently recognized. Myxoedema is characterised by low basal metabolism, and swelling which may result from proteins in the body fluids.

All races appear to be equally susceptible to lack of iodine, but the thyroid gland of Japanese is said to be much smaller than that of Europeans. Rush and Jones (1925) found the distribution of goitre to be generally parallel in whites and Indians, except in the northwestern states where the Indian diet contains more iodine, from the salmon fisheries. Goitrous enlargement of the thyroid is much more frequent in women than men.[3] Riebold (1915) collected sixty-five cases of goitre, 78 per cent of which were in females. From the study of nine pedigrees he concluded that it is inherited as a Mendelian character, dominant in females and recessive in males. But his pedigrees show cases where a male who must be heterozygous has the disease.

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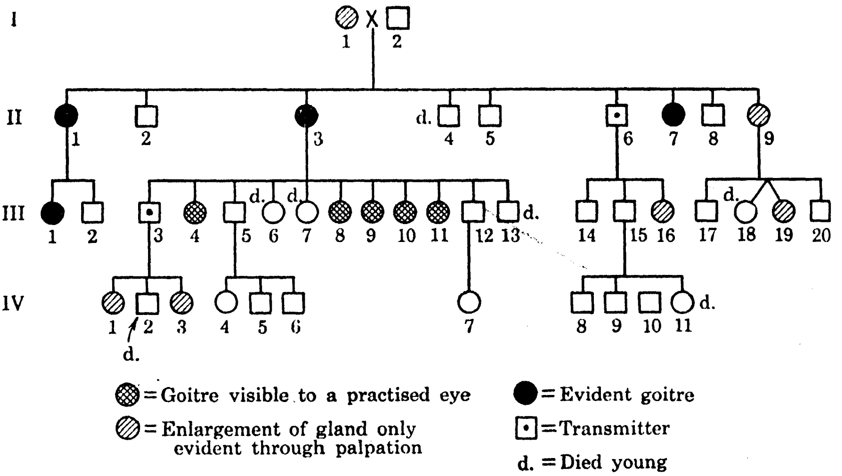
[3] This also applies to negroes, mulattoes and Indian-white mixtures in São Paulo, Brazil (Spix and Martius, 1824). Greenwald (1945) brings considerable evidence for the view that goitre was not endemic among the Indians and that it has only appeared in North and South America and in the Maoris of New Zealand since their contact with Europeans. He also concludes that it was introduced from N. Italy to Derbyshire in 1717. After first contact the disease is severe, later becoming milder. This, as well as the experiments in India, suggests that a virus may be involved. Forbes (1870) states that the Aymara Indians on Lake Titicaca used dried seaweed from the coast to cure goitre.

Figure 205 is from one of Bluhm's (1922) pedigrees, showing transmission in milder form by unaffected males in two cases. The father of I. 1 belonged to a Dutch family and lived in Heidelberg, on the edge of a goitre region, until twenty-two years of age. Case I. 1 married an officer in Westphalia and lived there in a region free from goitre. The daughter, II. 1, married an East Prussian officer. She had a goitre as large as a child's head, and lived in Berlin in her old age, dying at ninety. Her daughter, III. 1, also lived in goitre-free East Prussia until thirty, but developed the disease. In this pedigree only females show the disease, and its onset is not before middle life.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1 2
d.
d.
d.
d.
d.
d.
d.
▩ = Goitre visible to a practised eye
▨ = Enlargement of gland only evident through palpation
● = Evident goitre
⊡ = Transmitter
d. = Died young

Fig. 205. Pedigree of goitre. (After Bluhm)

In eight families of Bluhm and Siemens one affected and three normal males transmit, while four normal and sixteen affected females transmit. Siemens held goitre to be due to one dominant sex-limited factor.

Pfaundler (1924), from his collection of pedigrees, concluded that in some the inheritance was dominant and in others recessive. Brain (1927) found the same in England. A "dominant" pedigree with 8 cases (7 ♀ 1 ♂) in four generations, from Northamptonshire, is shown in Fig. 206. The six pedigrees show twenty-four females and two males affected, apparently dominant but with occasional skips Where endemicity is low only females may be affected, where it is high the sex-ratio of affected may even reach equality. Brain suggested that females transmit more frequently because of the influence on the foetus of thyroid disturbance in the mother. A survey of the school children in Northamptonshire in 1924 showed that 1.5 per cent of the boys and 7.6 per cent of the girls in urban districts were affected, 4.2 per cent of the boys and 10.2 per cent of the girls in rural districts. Even in endemic areas certain families have a much higher incidence than the general population, and there is no sharp distinction between endemic and sporadic goitre. Members of endemic families can develop goitre even though born and reared in non-endemic areas. In some areas the affected females outnumber the males 8 : 1.

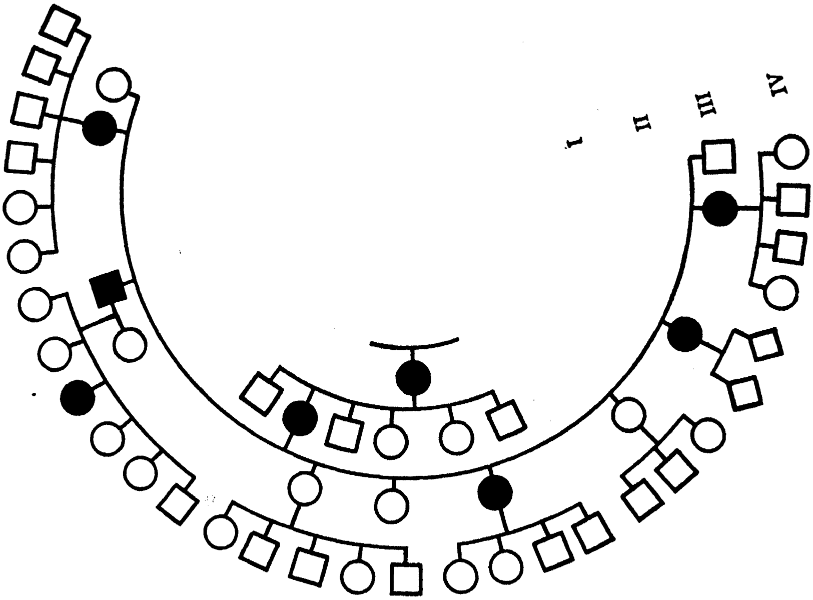

Fig. 206. Pedigree of endemic goitre. (After Brain)

Brain (1927) described five families in the London area in which goitre and congenital deaf mutism were associated in every case. The parents and relatives were always normal but it is not stated if they were related. In affected sibships there were 12 affected : 11 normal. This is probably a case of genetic linkage, both the goitre and the deaf mutism being regarded as recessive.

Milligan (1926) examined the school children of Bath and Glossop for goitre, finding 8 per cent incidence for girls and 2.2 per cent for boys. In one family in four generations there were twenty affected females to one affected male, the condition becoming almost sex-limited. Normal sons transmitted goitre to all five of their daughters. A survey of English school children about twelve years of age (Stocks, 1928) shows that the sex-ratio of incidence falls from *ca.* 5 : 1 in areas nearly free from goitre to 2 : 1 where the prevalence in boys is 10 per cent and then gradually to unity in endemic regions of high incidence. The main area of high incidence forms a belt from Cornwall north-east through Somerset to Northamptonshire and Derbyshire and up the Pennines. The highest incidence is where the Devonian, Triassic or Carboniferous formations outcrop.

Stocks and Karn (1927) concluded from the statistics of a large-scale survey of boys and girls in England, that a possible relationship exists between the prevalence of thyroid enlargement and cancer mortality, similar to that found in Swiss and American statistics but less pronounced. A survey of goitre occurrence in parts of Tipperary County, Ireland, in a thousand children of each sex between the ages of four and fourteen years, gives a total incidence of *ca.* 65 per cent, equal in boys and girls, contrary to the usual excess of affected girls. This condition can probably be explained by the extreme dearth of iodine in this area.

Lloyd (1924) studied the incidence of goitre in St. Louis and Chicago. At St. Louis 100 unselected patients with goitre had 2781 relatives, 8.9 per cent of whom were goitrous compared with 3 per cent in the whole population. One hundred patients in Chicago *with a family history* had 38 per cent of goitrous relatives. In 40.8 per cent of cases goitre was accompanied by tonsillitis or seasonal sore throat. Twenty per cent of the children of goitrous mothers were affected, but there were no cretins.

Bauer (1926) studied the particular form of goitre known as *struma nodosa colloides* in the Harz Mountains of Germany, an area of endemism. He collected 50 pedigrees containing 1463 persons with 172 cases of struma. The sex ratio of the affected was 4 ♀ : 1 ♂. With increasing severity of symptoms this ratio approaches 1.6 : 1. Aschner (1926) showed that Bauer's results involved statistical errors. He did not show that struma is a single unit nor that it is dominant. In a histological study of 466 thyroid glands, Schmid (1940) found that the weight curve had two peaks — one at puberty and one in old age, but there was no apparent influence of constitution on the histological structure of the goitre.

An extensive study of endemic goitre near Zürich, with many pedigrees, was made by Eugster (1934, 1935). He found from 12,000 records that inbreeding in the villages did not increase the incidence of goitre. The later-born in a sibship showed a higher incidence than the first-born. When a goitrous woman moves to a non-endemic area, later-born children have less goitre and vice versa. This is attributed to a plasmatic effect. The second part of this paper contains further extensive records and pedigrees, but the conclusion that endemic goitre is environmentally determined and not hereditary is unjustified in view of other results which show that some are more susceptible than others. Part III is a study of 520 pairs of twins, in which he could find no certain difference in degree of discordance between MZ and DZ twins. If living under different conditions, both MZ and DZ showed greater discordance, and the age of separation (early or late) was important. The condition of the thyroid at birth was found to be significant in connection with later resistance to goitre.

Eugster (1938) has made a similar study of endemic cretinism in the Swiss cantons of Aargau and Zürich. He found that the high or low frequency of cretinism in particular areas ran parallel with that of goitre. While he agrees that hypothyroid activity is an elementary pathological factor in the production of endemic cretinism, he denies that heredity is involved, although admitting that constitution plays a part in determining the localization and form of goitre. He finds numerous cases of cretinous children from non-goitrous parents, but no case of cretinism born in a goitre-free area and no higher consanguinity in the parents of cretins than in the general population. He also states that while immigrants to a cretinous area do not develop cretinism, their descendants in the second or even the first generation may do so. His twin studies are open to question. For example, the first pair, Gertrud and Anna, are so dissimilar at one year of age that it is difficult to believe they are MZ even though both have a peculiar hypothenar pattern of the hands. Moreover, they are listed as discordant, whereas Anna was clearly cretinous at one year but outgrew it, while Gertrud was normal at one year but at eighteen was a cretinous dwarf. A typical cretin, fifty-one years old, is shown in Fig. 207. He is a dwarf, 136 cm. tall, speechless, with a broad saddle-nose, wrinkled face and typical cretin gait.

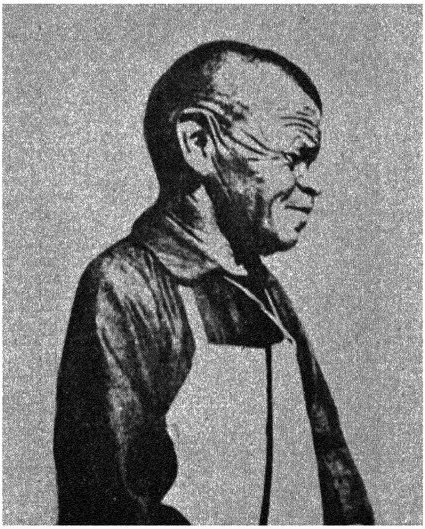

Fig. 207. Typical cretinous dwarf. (After Eugster)

De Quervain and Wegelin (1936) point out that cretinism is largely confined to countries with severe goitre morbidity, and that although England has goitrous areas it is free from endemic cretinism. They regard the connection between cretinism and goitre as proved. Figure 208 shows two feebleminded cretins, aged twenty-two and twenty-one from the Darenth Colony, Dartford, England. A complete lack of thyrotropic function, beginning in ante-natal development, damages the brain beyond repair.

Plattner (1938) made an anthropometric study of the hands of 107 non-goitrous male and female cretins. The hands are notably short, broad and stumpy, corresponding in size with those of a thirteen-to-fourteen-year-old boy and a ten-to-eleven-year-old girl respectively. In a later biometric study (Plattner, 1940) of the cretin nose (cf. Fig. 207), he finds that its length is that of a European boy of twelve, resembling the adults of primitive races such as the New Caledonians, the Melanesians or the Semang

Pygmies. The root of the nose is low and broad, the bridge very short and broad, the tip broad like the pygmies and other primitive races, blunt and frequently retroussé, the nasal index of males being 80.64.

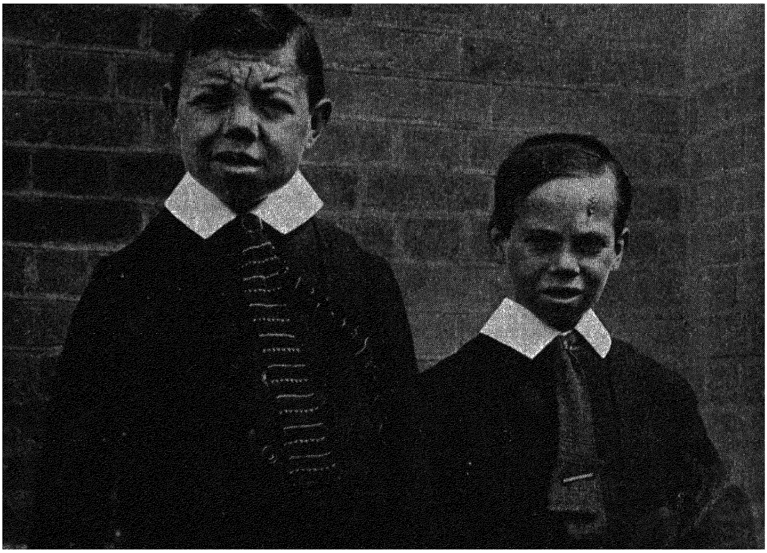

Fig. 208. Two feebleminded cretins, aged 22 and 21, from the Darenth Colony, Dartford.

Endemic cretinism is seldom seen in America, but Shelton (1931) described a family of two boys and two girls in California. The mother was born near Belanzona, Switzerland, which was notorious for its goitrous cretins. Her hypothyroidism takes the form of hayfever or asthma which is overcome by taking thyroid. The children show neither goitre nor myxoedema but are subnormal in size, with lordosis, prominent abdomen, retroussé noses, malocclusion and other defects which respond to thyroid. Unterrichter (1938) states that in one canton of the Tyrol, ten years of iodine salt prophylaxy extinguished the goitre and reduced the cretinism with its associated malformations from 1.5 to 0.4 per cent.

Goodkind and Higgins (1941) studied twenty-three cretins in Boston who had received thyroid for five to twenty-four years. The thyroid treatment of twenty-one was omitted for eight weeks. They were tested and showed increasing hypothyroidism and increased cholesterol in the blood. In I.Q. they ranged from over 100 to below 70, but the degree of mental defect did not correspond with the degree of thyroid deficiency. They conclude that the mental defect is not due to lack of thyroid but is congenital and a separate effect of the same hereditary cause. Thus, as has long been known, thyroid feeding may quicken the mental processes of cretins but cannot make good a congenital mental defect.

Bronstein, Bower and Murphy (1943) describe two boys (brothers), typical cretins in Chicago, aged thirteen and twenty-two years. Four sibs were normal. A sister and two of the mother's first cousins had thyroidectomies and the mother's sister had an enlarged thyroid. They cite several other familial cases of cretinism in the United States.

Davenport (1932) made an important study of endemic goitre in a mountain valley of western Maryland. Nine extensive pedigrees were collected, with a total of 297 cases (75 ♂ 222 ♀) in four generations. The analysis of these pedigrees has led to a hypothesis of inheritance which fits the facts better than any previous one. He assumes a gene $\mathbf{X^1}$ in the X-chromosome, which renders the female especially subject to thyroid enlargement, particularly at puberty, menstruation and pregnancy; and a gene **A** in an autosome, which has a similar effect, in both sexes, being responsible for imperfect construction or chemical action of the thyroid. Both genes are dominant and goitre develops only in the presence of both. This hypothesis agrees with the complicated inheritance in the pedigrees. Analysis shows that goitrous females will be $\mathbf{X^1X^1AA}$, $\mathbf{X^1X^1Aa}$, $\mathbf{X^1XAA}$ or $\mathbf{X^1XAa}$, while goitrous males will be $\mathbf{X^1YAA}$ or $\mathbf{X^1YAa}$. Some of the other results are shown in Table 17.

TABLE 17

GOITROUS GENOTYPES AND THEIR OFFSPRING

$\mathbf{X^1X^1AA} \times \mathbf{X^1YAA} = F_1\mathbf{X^1X^1AA}$ ♀ $\mathbf{X^1YAA}$ ♂, all goitrous.
$\mathbf{X^1XAa} \times \mathbf{X^1YAa} = F_1$ ♀ ♀ 3 aff. : 1 norm. ♂ ♂ 3 aff. : 5 norm.
$\mathbf{X^1X^1Aa} \times \mathbf{X^1YAa} = F_1$ ♀ ♀ 3 aff. : 1 norm. ♂ ♂ 3 aff. : 1 norm.
$\mathbf{XXaa} \times \mathbf{X^1YAa} = F_1$ ♀ ♀ 2 aff. : 2 norm. ♂ ♂ 1 aff. : 3 norm.
$\mathbf{X^1Xaa} \times \mathbf{X^1YAa} = F_1$ ♀ ♀ 1 aff. : 1 norm. ♂ ♂ 1 aff. : 1 norm.
$\mathbf{XXAa} \times \mathbf{X^1Yaa} = F_1$ ♀ ♀ 1 aff. : 1 norm. ♂ ♂ 0 aff. : – norm.
$\mathbf{XX^1aa} \times \mathbf{XYAa} = F_1$ ♀ ♀ 1 aff. : 3 norm. ♂ ♂ 1 aff. : 3 norm.

Various other combinations are possible. It will be seen that the proportions of affected males and affected females will vary widely according to the homozygous or heterozygous presence of these two dominant factors, one of which is sex-linked. Two normal parents may have a goitrous daughter or even goitrous children of both sexes. Further tests will show whether any of the supposed dominant or recessive pedigrees fail to conform to these rules.

Meulengracht (1933) described a family in Copenhagen in which two normal parents produced six daughters, all with goitre, and five sons, all normal. The mother had a goitrous sister. Such a result would be possible if the genetic composition of the parents corresponded with line six of Table 17, but improbable. He finds, contrary to other results, that endemic goitre is almost equally frequent in both sexes before puberty, and he is led to doubt the genotypic basis of sporadic goitre.

A pedigree of sporadic goitre, collected by Siemens (Brugsch and Lewy, 1926) contains nine cases, all females, in six generations, the inheritance always from mother to daughter. The condition in this family may be regarded as sex-limited.

Kemp (1933) reported a goitrous family of Dutch-English extraction in Long Island (a non-goitrous region) with seven cases, all female, in three generations. Of the adult daughters, there were six affected to one normal. On Siemens' theory of a dominant gene limited to females, only half the daughters should be affected. Kemp suggests a dominant gene in the X-chromosome which also causes non-disjunction of the XX in the female, together with sex-limitation. Females would then be XgXY, their egg cells XgX and Y. With X and Y sperm, the zygotes would be (1) XgXX, (2) XgXY, (3) XY, (4) YY. (1) and (4) might be lethal or sterile, (2) would give daughters transmitting goitre, while (3) would be normal sons. This is essentially like the linked $\widehat{XX}$ assumed in the Cunier pedigree (p. 28) except that he calls it *non-disjunction.* But why should every goitrous pedigree happen to show non-disjunction or linked XX? Exceptions could occur, as in Drosophila, giving Xg and XY or X and XgY. These with normal sperm would give (1) XgX, (2) XXY, (3) XX, (4) XgXY, (5) XgY, (6) XYY, (7) XY, (8) XgYY. Of these offspring, (2) and (3) would be non-goitrous females, (5) and perhaps (8) would be goitrous males. It is clear that still more pedigrees are necessary to settle these questions.

There are curious physiological relations between iodine and another halogen, *fluorine.* In support of an antagonism between them, May (1935) found that in rats fed iodine the thyroid had its follicles filled with colloid, the connective tissue in the gland being reduced. After administering fluorine, the follicles were small, with little colloid, and the connective tissue increased. He applied fluorine therapy to goitrous patients to produce hypoplasia of the thyroid. Endemic fluorosis (mottled enamel) is described in many parts of the world with waters having one part of fluorine per million. Stiff back and elbows occur when the fluorine reaches three parts per million. Wilson (1939) points out that dental fluorosis occurs in Essex, Somerset, Derbyshire and other parts of England. He also (1941) shows that the distribution of endemic goitre in the Punjab and in England is related to the geological distribution of fluorine and of dental fluorosis. The plains of the Punjab have long been known as a centre for endemic goitre and cretinism, and they show a high degree of dental fluorosis. Both these conditions are present also in the school children of two areas in Somerset, while in an adjacent area both are absent. In such areas, iodine in the soil waters must be replaced by fluorine. Fluorine is one of the trace elements, necessary for nutrition. The absolute iodine content of the soil water is not the only factor in endemic goitre. Something else must determine the availability of the iodine for the human organism. In the thyroid it first forms 3:5-diiodotyrosine, which is then converted into thyroxine. This is finally stored in the form of thyroglobulin or colloid, the secretion of which controls the rate of metabolic processes.

Exophthalmic Goitre

This condition, also known as *Graves' disease*, *Basedow's disease*. *thyrotoxicosis* and *hyperthyroidism*, was only described at the beginning of the nineteenth century. It is characterised by an enlarged thyroid, rapid pulse, exophthalmia (eyes protruding) and other symptoms. Emaciation results, and an increased basal metabolism. Lesions of the sympathetic nervous system are believed to be concerned in producing the excessive thyroid activity.

Campbell (1925) found that, although it is not supposed to be endemic, the disease is most common in Cornwall, Devon, Somerset, parts of Wales, Westmoreland and parts of Lancashire and Yorkshire, which correspond at least in part with the areas of endemic goitre. In Scotland one man dies of it for every ten women; in Ireland the ratio is 1 : 7, and the birth rate is lower where the disease is prevalent. Read (1939) has studied the incidence of Graves' disease in the United States. He finds on the contrary that its occurrence is more or less uniform and that it occurs in regions where endemic goitre is unknown. Reveno (1931) developed the view that exophthalmic goitre results from a long-continued toxic process in the intestinal tract. This damages the thyroid, causing destruction of its tissue and producing faulty metabolism of tyrosine, which results in an excess of its derivatives, thyroxine, epinephrine and tyramine.

Bram (1929) concludes from a study of over four thousand cases that the disease syndrome is neither goitre nor purely a disease of the thyroid. He lists seven symptoms which should be present and finds twenty-six different forms of the disease. As exophthalmos and goitre may occasionally both be absent, this name should be dropped. A pedigree (Fig. 209) by Prissmann (1929) shows 12 cases (11 ♀ 1 ♂) in four generations, associated with marked nervousness, tuberculosis, mental defect and artistic nature. Case IV. 1 was sixty-eight, and never showed any symptoms of hyperthyroidism, yet he transmitted it to half his children. Presumably his sex hormones prevented its expression. The pedigree indicates a dominant with expression chiefly in the female sex. Martin (1939) regards thyrotoxicosis as having two main components, (1) thyroid overactivity or dysfunction, (2) instability of the autonomic nervous system. He studied thirteen ♀ cases. One patient's family had 7 cases (2♂ 5♀) in two generations, the grandparents both being normal. Shillington (1945) cites a family with extreme *congenital exophthalmos* in the mother, two sons and a daughter.

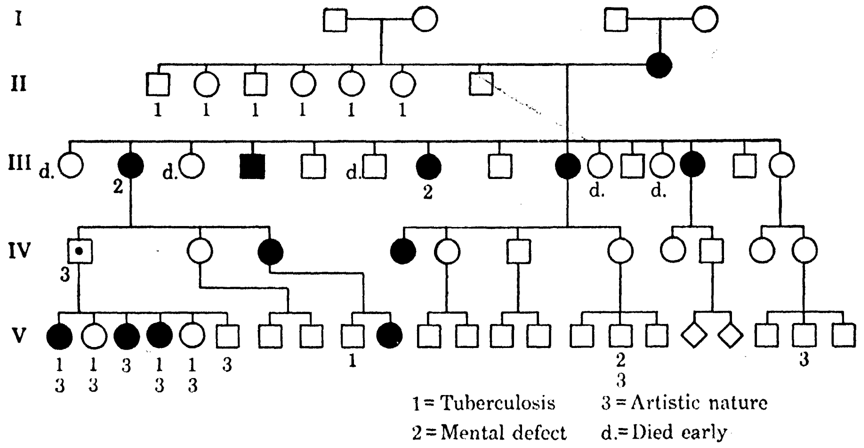

Fig. 209. Pedigree of Basedow's disease, exophthalmic goitre. (After Prissmann)

Bram (1933) later investigated 220 cases of Graves' disease without rise in basal metabolism or loss of weight. He concludes that Graves' disease and hyperthyroidism are not synonymous terms, and that the former may occur without thyroid excitation. Lehmann (1937) finds that in pedigrees of hyperthyroidism all degrees may occur from mild forms to those with tachycardia, protruding eyes,[4] tremor of the hands, great excitability and increased metabolism.

[4] Smelser (1937) finds exophthalmos due to excess orbital tissue in the cases examined. The connective tissue, fat and muscles were oedematous and conditions were similar in hyper- and hypothyroid cases. He produced exophthalmos in guinea pigs by injecting anterior pituitary. Removal of the cervical sympathetic did not inhibit the increase in orbital tissues. In further papers, Smelser (1939) finds that not only the orbital fat and connective tissue, but also the body fat is affected (to a lesser degree) by injecting pituitary extract. Also (1943) the hypertrophy of the extraocular muscles and the orbital fat is due to increase in water content.

Rundle and Wilson (1944) find that the ophthalmoplegia in Graves' disease is generally bilateral and depends primarily on weakness of the superior rectus muscle. Rundle and Pochin (1944), in a study of seventeen human cases, find that the exophthalmia is accounted for quantitatively by increase in the retro-bulbar tissues. The fat content of the eye muscles was doubled. Pochin (1944) finds that in growing guinea pigs exophthalmia can be produced in 48 hours by injections of ante-pituitary. This was due to oedema of orbital tissues, especially the dorsal lachrymal gland. He concludes that the relative increase in water content is due to decrease in the fat content of the wasting muscles. Exophthalmos has generally been attributed to excess of thyrotropic hormone (not thyroxin).

The dominance is often irregular and females are much more frequently affected than males. In a later paper (1938) he reports 29 pedigrees with 108 cases and 15 pairs of twins. These results support the hypothesis of one dominant factor which shows weak expression in the male sex. The 19 cases in men show reduced symptoms in 11. Several degrees of the disease exist in both sexes and are believed to be due partly to modifying genes and partly to environmental influences.

In a series of 332 patients with goitre, Rundle (1941) found that 22 per cent had a family history of thyroid disease, i.e., toxic goitre (Basedow's disease), hyperthyroidism, myxoedema or simple goitre. Psychic trauma is frequently associated with the onset of symptoms and exophthalmia can develop without other symptoms. One family shows three cases of goitre and three of toxic goitre (all females) in three generations. The genetic relation between these two forms of goitre requires further investigation. Steiner (1936) described a pair of MZ female twins, forty years of age, one of whom developed Basedow's disease and the other thyrotoxicosis at the same time.

Bartels (1941) has recently examined the whole question of the inheritance element in the various thyroid diseases. From numerous pedigrees and case records, Graves' disease is only recorded in three generations in one family. He thinks the condition shows pronounced sex-limitation, but not sex-linkage, and is unable to decide between polymeric factors, irregular dominance or recessive inheritance. He rejects the theory that Graves' disease corresponds with a hyperthyroid and *myxoedema* with a hypothyroid constitution. In myxoedema the connective tissues are swollen and the skin dry. In families with Graves' disease, simple goitre and myxoedema often occur, so there is probably a genetic connection between these thyroid affections, all of which have an inheritance element, but the manner of inheritance of myxoedema cannot be stated. It is regarded as established that goitre and Graves' disease can be due to the same hereditary disposition, which can also probably develop myxoedema. Bartels thinks sex-linkage can be excluded, but that a simple recessive gene is involved, with sex-limitation to women and a penetrance of 70 to 80 per cent. Toxic adenoma of the thyroid is regarded as toxicosis in an existing goitre, hence hereditary or not according to the nature of the goitre. While hereditary disposition plays a part in endemic goitre, congenital goitre and endemic cretinism are regarded as non-hereditary. Sporadic goitre is found to be inherited in the same way as Graves' disease. Schmidt and Hertzler (1942) regard cardiotoxic goitre as a distinct entity in which the thyrotoxicosis results from a perverted thyroid secretion.

Riddle (Carnegie Year-Book, 1942) finds that the eggs of goitrous female pigeons take two to three days longer to hatch. The young from goitrous females have large thyroids at hatching. Iodine in the diet is effective.

Eugster (1942) made an extensive study of the type of capillaries at the base of the finger-nail in goitrous and non-goitrous members of families in areas of endemic goitre in Switzerland. From a comparison also of identical twins, he concludes that peculiar types of capillary form are probably not produced by the goitre.

Eckes, Glasser and Mersheimer (1943) describe juvenile hyperthyroidism in three sisters and their cousin. Sutphin, Albright and McCune (1943) describe an Italian family with idiopathic *hypoparathyroidism.* The parents were first cousins and three of ten children were affected. These three also had Monilia infection, and these two conditions were also associated in two unrelated cases. The three sibs, their father and some of the other sibs also had hypochromic polycythemia. The conditions suggest that hypoparathyroidism is recessively inherited and accompanied by or linked to Monilia susceptibility. It is characterised by high calcium excretion and high phosphorus content in the blood.

LITERATURE

Abbott, L. D. F., Jr. 1941. Alkaptonuria in a negro family. *Science* 94:365–366.

Abderhalden, E. 1903. Familiäre Cystindiathese. *Zeits. f. Physiol. Chem.* 38:557–561.

Allan, F. N. & Rowntree, L. G. 1931. The association of diabetes insipidus and diabetes mellitus. *Endocrinol.* 15:97–106.

Allen, F. M. & Mitchell, J. W. 1920. A case of hereditary diabetes. *Arch. Int. Med.* 25:648–660.

Althausen, T. L. & Kerr, W. J. 1933. Hemochromatosis II. *Endocrinology* 17:621–646. Figs. 4.

Anderson, J. P. 1933. Hereditary Gaucher's disease. *J. Am. Med. Assn.* 101:979–981.

Aschner, Berta. 1926. Bemerkungen zu Bauer's Arbeit. *Bruns' Beitr. z. Klin. Chir.* 137:179–181.

Ashby, H. T. 1926. Haematoporphyria congenita: its association with hydroa vacciniforme and pigmentation of the teeth. *Quart. J. Med.* 19:375–379.

Bagnall, E. S. 1929. Alkaptonuria. *New Engl. J. Med.* 201:422–423.

Barach, J. H. 1926. Constitutional and hereditary traits in diabetes. *Am. J. Med. Sci.* 172:243–248.

Barraquer, L. 1907. Histoire clinique d'un cas d'atrophie du tissu celluloadipeaux. *Neurol. Zentlbl.* 26:1072.

Barraquer-Ferré, L. 1935. Lipodystrophie progressive. *Presse Méd.* 43:1672–1674. Figs. 2.

Bartels, E. D. 1941. *Heredity in Graves' Disease.* Copenhagen. Pp. 384.

Bauer, J. 1922. Über Fettansatz. *Klin. Wochens.* 1:1977–1983.

———. 1941. Obesity. *Arch. Int. Med.* 67:968–994.

Bauer, K. H. 1926. Untersuchungen über die Frage einer erbkonstitutionellen Veranlagung zur Struma nodosa colloides. *Bruns' Beitr.-z. Klin. Chir.* 135:512–568.

Beadle, G. W. & Tatum, E. L. 1941. Genetic control of biochemical reactions in Neurospora. *Proc. Nat. Acad. Sci.* 27:499–506.

Bennett, T. I., Hunter, D. & Vaughan, J. M. 1932. Idiopathic steatorrhoea (Gee's disease). *Quart. J. Med.* 25:603–677. Pls. 9.

Berg, H. T. 1939. The genetic aspect of diabetes mellitus. *J. Am. Med. Assn.* 112:1091.

Beumer, H. & Wepler, W. 1937. Über die Cystinkrankheit der ersten Lebenszeit. *Klin. Wochens.* 16:8–10. Figs. 3.

Bigler, J. A. 1939. Loss of subcutaneous fat of the lower extremities. *J. Am. Med. Assn.* 112:627–628. Figs. 2.

Blatherwick, N. R. 1934. Tyrosinosis: a search for additional cases. *J. Am. Med. Assn.* 103:1933.

Bloem, T. F., Groen, J. & Postma, C. 1936. Gaucher's disease. *Quart. J. Med.* 29:517–527. Pls. 4.

Bloom, D., Kaufman, S. R. & Stevens, R. A. 1942. Hereditary xanthomatosis. *Arch. of Derm. & Syph.* 45:1–18. Figs. 8.

Blotner, H. 1942. The inheritance of diabetes insipidus. *Am. J. Med. Sci.* 204:261–265.

Bluhm, Agnes. 1922. Zur Erblichkeit des Kropfes. *Arch. f. Rass. u. Ges.-Biol.* 14:1–9.

Bock, J. C. 1944. The benign meliturias. *Physiol. Revs.* 24:169–176.

Bowcock, H. M. 1929. Familial glycosuria, report of a large family. *Ann. Int. Med.* 2:923–931.

Brain, W. R. 1927. Heredity in simple goitre. *Quart. J. Med.* 20:303–319.

Bram, I. 1929. Types of Graves' disease. *Endocrinol.* 13:164–180. Figs. 19.

———. 1933. Exophthalmic goitre without increased basal metabolic rate. *Endocrinol.* 17:23–28. Figs. 5.

Brice, A. T. 1932. Tryptophanuria and its significance. *Arch. Int. Med.* 49:978–980.

Brill, N. E., Mandelbaum, F. S. & Libman, E. 1905. Primary splenomegaly — Gaucher type. *Am. J. Med. Sci.* 129:491–504. Figs. 8.

Bronstein, I. P., Bower, L. E. & Murphy, J. 1943. Familial cretinism. *Am. J. Med. Sci.* 205:114–117. Figs. 2.

Brugsch, Th. & Lewy, F. H. 1926. *Allgemeiner Teil der Personallehre.* Berlin.

Bulloch, W. 1909. Diabetes insipidus. *Treas. Hum. Inheritance.* Part 1:1–6. Pl. 1.

Camerer, J. W. 1935. Eine Ergänzung des Weilschen Diabetes-insipidus Stammbaumes. *Arch. f. Rass. u. Ges.-Biol.* 28:382–383.

Cammidge, P. J. 1928. Diabetes mellitus and heredity. *Brit. Med. J.* ii. 738–741.

———. 1934. Heredity as a factor in the aetiology of diabetes mellitus. *Lancet* 226:393–395.

Cammidge, P. J. & Howard, H. A. H. 1926. Seven cases of essential pentosuria. *Brit. Med. J.* ii. 777–779.

——— ———. 1930. The hereditary transmission of hypoglycaemia in mice. *Proc. Roy. Soc. Med.* 23:1341–1343.

Campbell, J. M. H. 1925. The geographical distribution of exophthalmic goitre in the British Isles. *Quart. J. Med.* 18:191–223.

Chandler, F. G., Harrison, G. A. & Rimington, C. 1939. Clinical porphyrinuria, with report of a case of the acute idiopathic type. *Brit. Med. J.* ii. 1173–1180.

Chase, L. A. 1927. Hereditary diabetes insipidus. *Can. Med. Assn. J.* 17:212–214. Figs. 3.

Clare, N. T. & Stephens, E. H. 1944. Congenital porphyria in pigs. *Nature* 153:252.

Cockayne, E. A. 1931. Lipodystrophia progressiva. *Proc. Roy. Soc. Med.* 31:1344–1345. Figs. 4.

———. 1933. Congenital steatorrhoea. *Lancet* 225:1086–1087.

Coggeshall, C. & Root, H. F. 1940. Acromegaly and diabetes mellitus. *Endocrinol.* 26:1–25.

Cole, V. V., Harned, B. K. & Keeler, C. E. 1941. Inheritance of glucose tolerance. *Endocrinol.* 28:25–32.

Cowen, M. 1936. Erblichkeits- und Konstitutionsstudien an 54 Zuckerkranken. *Arch. J. Klaus-Stift.* 11:281–368.

van Creveld, S. 1934. Investigations on glycogen disease. *Arch. of Dis. of Child.* 9:9–26.

———. 1939. Glycogen disease. *Medicine* 18:1–128.

Currier, F. P. & Davis, D. B. 1930. Progressive lipodystrophy appearing at menopause. *Am. J. Med. Sci.* 179:750–758. Figs. 5.

Danis, P. G. & Rossen, J. A. 1941. Renal rickets. *J. Paediat.* 18:103–116. Figs. 9.

Darnall, J. R. 1935. Haemochromatosis: review of the literature and report of three cases. *Ann. Int. Med.* 8:1121–1137. Figs. 3.

Davenport, C. B. 1932. The genetical factor in endemic goitre. *Carnegie Publ.* No. 428. Pp. 56.

Davidenkov, S. 1940. Inherited inability to eat sugar. *J. of Hered.* 31:5–7.

Dercum, F. X. 1892. Three cases of a hitherto unclassified affection resembling in its grosser aspects obesity, but associated with special nervous symptoms — adiposa dolorosa. *Am. J. Med. Sci.* 104:521–535. Figs. 6.

Dickenson, W. H. 1875. *Diseases of the Kidney.* London.

Draper, G., Dupertuis, C. W. & Caughey, J. L. 1940. The differentiation by constitutional means between pancreatic diabetes and diabetes of pituitary origin. *Trans. Assoc. Am. Physic.* 55:146–154. Figs. 3.

Duncan, G. G. 1942. *Diseases of Metabolism.* Philadelphia & London: Saunders. Pp. 985.

Eaves, E. C. 1930. Diabetes insipidus. *Brain* 53:47–55. Pl. 1.

Eckes, W. P., Glasser, S. T. & Mersheimer, W. L. 1943. Hyperthyroidism of the juvenile familial type. *Am. J. Surgery* 61:291–296. Figs. 5.

Ellis, R. W. B. & Payne, W. W. 1936. Glycogen disease (von Gierke's disease; hepato (nephro) megalia glycogenica). *Quart. J. Med.* 29:31–49. Pls. 2.

Ellis, R. W. B. & Tallerman, K. H. 1934. Obesity in childhood. *Lancet* 227:615–620. Figs. 5.

Emanuel, E. 1941. Gaucher's disease: report of two unrelated cases. *Edinb. Med. J.* 48:843–852. Figs. 4.

Engelberg, H. & Newman, B. A. 1943. Xanthomatosis a cause of coronary artery disease in young adults. *J. Am. Med. Assn.* 122:1167–1170. Figs. 7.

Enklewitz, M. & Lasker, M. 1933. Studies in pentosuria. *Am. J. Med. Sci.* 186:539–548.

Eugster, J. 1934. Zur Erblichkeitsfrage der endemischen Struma. *Arch. J. Klaus-Stift.* 9:275–363.

———. 1935. Genetische Untersuchungen über die Ursachen des Kropfes. *Arch. J. Klaus-Stift.* 10:101–192. Peds. 63.

———. 1936. Die Zwillingsstrume. *Arch. J. Klaus-Stift.* 11:369–539. Figs. 74.

———. 1937. Kropfproblem und Bodenatmung, *Arch. J. Klaus-Stift.* 12:27–32.

———. 1938. Zur Erblichkeitsfrage des endemischen Kretinismus. *Arch. J. Klaus-Stift.* 13:383–494. Figs. 72.

———. 1942. Endemische Thyreopathie und Kapillarbild, mit besonderer Berücksichtigung der Erbbiologie. *Arch. J. Klaus-Stift.* 17:1–80. Many figs.

Eyster, W. H. 1924. Inherited deficiency in carbohydrate metabolism in maize. *Bot. Gazette* 78:446–452. Figs. 3.

Fasold, Anna. 1924. Studien über Vererbung von Hautkrankheiten. VI. Xanthom (Cholesterosis cutis). *Arch. f. Rass. u. Gen.-Biol.* 16:54–66.

Figge, F. H. J. 1944. Fluorescence studies on cancer. *Cancer Res.* 4:465–471. Pl. 1.

Finke, W. 1930. Über Diabetes mellitus als Erbkrankheit und seine konstitutionelle Beziehungen zu anderen Krankheiten. *Zeits. f. Klin. Med.* 114:713–738.

Forbes, D. 1870. On the Aymara Indians of Bolivia and Peru. *J. Ethnol. Soc. Lond.* N.S. 2:193–305. Pls. 7.

Fourie, P. J. & Rimington, C. 1937. Living animal cases of congenital porphyrinuria. *Nature* 140:68.

*Frisch, A. V. 1922. (Familial bronzing.) *Wien Arch. f. inn. Med.* 4:149–166.

Gänsslen & Fritz. 1924. Über Diabetes insipidus. *Klin. Wochens.* 3:22–23.

Gardner, E. & Simpson, K. 1938. Sudden death from von Gierke's (glycogen) disease. *Lancet* 234:659–661.

Garrod, Sir Archibald. 1923. *Inborn Errors of Metabolism.* 2nd ed.

———. 1936. Congenital porphyrinuria. *Quart. J. Med.* 29:473–480.

Gaucher. 1882. Splenomegalie primitive, epithelioma primitif de la rate. Doctor's thesis.

Georgopoulos, M. 1933. Über die Azotämien der Weilschen Krankheit und des Schwarzwasserfiebers. *Deut. Arch. Klin. Med.* 175:60–73.

Gibson, R. B. & Fowler, W. M. 1936. Infantilism and diabetes mellitus. *Arch. Int. Med.* 57:695–707. Figs. 3.

von Gierke, E. 1929. Hepato-Nephromegalia glykogenica. *Beitr. z. path. Anat.* 82:497–513. Pl. 1, fig. 1.

Goodkind, R. P. & Higgins, H. L. 1941. Hypothyroidism in infants and children. *N. Engl. J. Med.* 224:722–726.

Gordon, M. B. 1922. Childhood myxedema or so-called sporadic cretinism in North America. *Endocrinology* 6:235–254.

Gossage, A. M. 1908. The inheritance of certain human abnormalities. *Quart. J. Med.* 1:331–347. Figs. 10.

Gould, J. N. & Thomas, T. G. 1943. The diagnosis of alkaptonuria. *Brit. Med. J.* i. 788.

Graham, S. & Hutchinson, J. H. 1941. Familial renal dwarfism. *Arch. of Dis. in Child.* 16:253–256.

Gram, H. C. 1932. The heredity of oxalic urinary calculi. *Acta Med. Scand.* 78:268–281.

Graves, R. C. 1922. Diagnosis of shadowless renal calculi. *Ann. of Surg.* 75:487–491. Pl. 1.

Gray, A. M. H. 1926. Haematoporphyria congenita with hydroa vacciniforme and hirsuties. *Quart. J. Med.* 19:381–391. Pl. 1.

Greenwald, I. 1945. The early history of goitre in the Americas, in New Zealand and in England. *Bull. Hist. Med.* 17:229–268.

Günther, Hans. 1922. Die Bedeutung der Haematoporphyrie in Physiologie und Pathologie. *Ergebn. allg. Path. u. Anat.* 20, i. 609–764.

Gurney, R. 1936. The hereditary factor in obesity. *Arch. Int. Med.* 57:557–561.

Guthrie, L. G. 1902. "Idiopathic" or congenital human abnormalities. *Lancet* 1. 1243–1246.

Hanhart, E. 1939. Nachweis der ganz vorwiegend einfach-rezessiven Vererbung des Diabetes mellitus. *Der Erbarzt.* 6:5–15.

Hanot, V. & Chauffard, A. 1882. Cirrhose hypertrophique pigmentaire dans le diabète sucré. *Rev. de Méd.* ii. 385–403. Figs. 2.

Harington, C. R. 1944. Thyroxine: its biosynthesis and its immunochemistry. *Proc. Roy. Soc.* 132B:223–238.

*Harper, M. H. 1938. Congenital steatorrhoea due to pancreatic defect. *Arch. Dis. Child.* 13:45.

Hartston, W. L. 1931. Gaucher's disease. *Proc. Roy. Soc. Med.* 31:1031–1032. Figs. 2.

———. 1933. Lipodystrophia progressiva. *Lancet* 225:1416–1418. Figs. 2.

Hatlehol, R. 1924. Blood sugar studies. *Acta Med. Scand.* Suppt. 8. Pp. 260.

Heeres, P. A. & Vos, H. 1929. Fructosuria. *Arch. Int. Med.* 44:47–64.

Heinbecker, P., White, H. L. & Rolf, D. 1944. Experimental obesity in the dog. *Am. J. Physiol.* 141:549–565. Figs. 8.

Hilton, E. L. G. & Eden, K. 1941. Xanthomatosis of the skeleton in an adult. *Lancet* 240:782–784. Figs. 3.

Hinsworth, H. P. 1936. Diabetes mellitus. *Lancet* 230:127–130.

Hinsworth, H. P. 1939. The mechanism of diabetes mellitus. *Lancet* 237:1–6, 65–68, 118–122, 171–176.

Hjärne, U. 1927. A study of orthoglycaemic glycosuria with particular reference to its hereditability. *Stockholm.* Pp. 149, figs. 3.

Hoffman, S. J. & Makler, M. I. 1929. Gaucher's disease: a review of the literature and report of a case diagnosed from section of an inguinal gland. *Am. J. Dis. Child.* 38:775–793. Figs. 2.

Hogben, L., Worrall, R. L. and Zieve, I. 1932. The genetic basis of alcaptonuria. *Proc. Roy. Soc. Edinb.* 52:264–295.

Holst, J. E. 1926. The occurrence of benign glycosuria in diabetic families. *Arch. Int. Med.* 38:279–291.

Horowitz, N. H, Bonner, D., Mitchell, H. K., Tatum, E. L. & Beadle, G. W. 1945. Genic control of biochemical reactions. *Amer. Nat.* 79:304–317.

Horsfall, F. L., Jr. & Smith, W. R. 1935. Schüller-Christian syndrome, lipoid granulomatosis with defects in the bones, exophthalmos and diabetes insipidus. *Quart. J. Med.* 28:37–51. Pls. 3.

Hurst, A. F. 1923. Hereditary familial congenital haemorrhagic nephritis. *Guy's Hosp. Rep.* 73:368–370.

Hurtley, W. H. & Garrod, A. E. 1913. Congenital family steatorrhoea. *Quart. J. Med.* 6:242–258.

Jacobsen, V. C. 1940. Levulosuria. A study of two cases in brothers. *Am. J. Med. Sci.* 200:304–310.

Jones, A. B. 1939. Schüller-Christian's disease: report of a case in one of identical twins. *Ann. Int. Med.* 13:1068–1075. Figs. 6.

Jones, H. W. & Nissler, C. W. 1925. Pentosuria. Report of five cases in one family. *Ann. of Clin. Med.* 4:505–509.

Joslin, E. P. 1940. *The Treatment of Diabetes Mellitus.* 7th edn. Philadelphia.

Kemp, Tage. 1933. The inheritance of sporadic goitre. *Human Biol.* 5:480–490.

Kennedy, S. 1931. Hereditary diabetes mellitus. *J. Am. Med. Assn.* 96:241–245.

*Keusch, M. 1936. *Cluj. Med.* 17:155–160.

Klüver, H. 1944. On naturally occurring porphyrins in the central nervous system. *Science* 99:482–484.

Konstam, G. & Gordon, H. 1936. Idiopathic steatorrhoea with skin lesions and megalocytic anaemia. *Proc. Roy. Soc. Med.* 29:629–631. Col. pl. 1.

Koref, O., Vargas, L., Jr., Rodriguez, F. H. & Telchi, A. 1944. Alloxantin as a diabetogenic agent in rabbits. *Endocrinology* 35:391–393.

Krebs, H. A. & Henseleit, K. 1932. Untersuchungen über die Harnstoffbildung in Tierkörper. *Zeits. Physiol. Chem.* 210:33–66.

*Kretschmer, H. L. 1916. Cystinuria and cystin stones. *Urol. Cutan. Rev.* 20:1–10.

Landis, H. R. M. 1921. Familial diabetes. *Trans. Assn. Am. Physicians* 36:293–295.

Landoff, G. A. 1940. Beitrag zur Xanthomatose der Knochen. *Acta Orthop. Scand.* 11:70–128.

Lasker, Margaret. 1941. Essential fructosuria. *Hum. Biol.* 13:51–63.

Lasker, M., Enklewitz, M. & Lasker, G. W. 1936. The inheritance of *l*-xyloketosuria (essential pentosuria). *Hum. Biol.* 8:243–255.

Lawrence, R. D. 1935. Haemochromatosis and heredity. *Lancet* 229: 1055–1056.

Leesmith, N. 1933. Three cases of familial hepatosplenomegaly. *Proc. Roy. Soc. Med.* 26:370–371.

van Leeuwen, H. C. 1933. Über familiäres Vorkommen von Lipodystrophia progressiva zusammen mit Otosklerose, Knochencysten und geistiger Debilität. *Zeits. f. Klin. Med.* 123:534–547. Figs. 6.

Lehmann, W. 1937. Zur Erbpathologie der Hyperthyreosen. *Zeits. f. Abst. u. Vererb.* 73:531–535.

———. 1938. Zwillings- und Familienuntersuchungen zur Erbpathologie der Hyperthyreose. *Zeits. Mensch. Vererb. Konst.* 22:182–223.

Lemser, H. 1938. Zur Erb- und Rassenpathologie des Diabetes mellitus. *Arch. f. Rass. u. Ges.-Biol.* 32:481–516.

Levit, S. G. & Pessikova, L. N. 1934. The genetics of diabetes insipidus. (Russian with English summary.) *Trudy Med.-Genet. Inst. Gorky.* 3:132–147.

———. 1936. The genetics of diabetes insipidus. *J. of Hered.* 27: 445–448.

Lewis, Aubrey. 1937. A study of cretinism in London. *Lancet* 232:1505–1509.

Lewis, H. B. 1932. The occurrence of cystinuria in healthy young men and women. *Ann. Int. Med.* 6:183–192.

Lignac, G. O. E. 1925. Stoormis der cystine-stofwisseling bij kinderen in verband met dierproeven. *Nederl. Tijdschr. v. Geneesk.* 69:819–827.

———. 1938. A syndrome consisting of affections of the kidney, stunted growth, rickets and disturbed cystine metabolism. *Am. J. Med. Sci.* 196:542–547.

Lindeboom, G. A. 1933. Beobachtungen bei einem Fall von Diabetes insipidus et mellitus. *Deut. Arch. Klin. Med.* 175:74–89.

Lindsay, L. M., Ross, A. & Wigglesworth, F. W. 1935. Von Gierke's glycogen disease. *Ann. Int. Med.* 9:274–281. Figs. 5.

Llewellyn, L. J. 1922. The aetiology of gout. *Lancet* 202:475–478.

Lloyd, Bess. 1924. Studies on the incidence and inheritance of goitre in St. Louis and Chicago. *Ann. Clin. Med.* 3:275–279.

McCarrison, R. 1909. Observations on endemic cretinism in the Chitral and Gilgit Valleys. *Proc. Roy. Soc. Med.* ii. (Med. Sect.):1–36. Figs. 10.

———. 1914a. Experimental researches on the etiology of endemic cretinism, congenital goitre, and congenital parathyroid disease. *Indian J. Med. Res.* 1:505–522. Figs. 24.

———. 1914b. An enquiry into the causation of goitre at the Lawrence Military Asylum, Sanawar. *Indian J. Med. Res.* 1:536–588.

———. 1930. A goitre survey in albino rats. *Brit. Med. J.* i. 989–992.

Mackey, L. & Garrod, A. E. 1922. On congenital porphyrinuria associated with hydroa aestivale and pink teeth. *Quart. J. Med.* 15:319–330. Pls. 2.

Mackey, L. & Garrod, A. E. 1926. A further contribution to the study of congenital porphyrinuria (haematoporphyria congenita). *Quart. J. Med.* 19:357–373. Col. pl. 1.

Macklin, M. T. 1934. Inherited anomalies in metabolism II. *J. of Hered.* 25:123–126.

Marañon, G. & Bonilla, E. 1925. A case of precocious and hereditary diabetes insipidus. *Endocrinology* 9:467–471. Fig. 1.

Marañon, G. & Soler, J. B. 1926. Progressive lipodystrophy and hyperthyroidism. *Endocrinol.* 10:1–16. Figs. 6.

Marble, A. 1932. Chronic essential pentosuria. *Am. J. Med. Sci.* 183:827–831.

———. 1932. Renal glycosuria. *Am. J. Med. Sci.* 183:811–827.

Margolis, J. I. 1929. Chronic pentosuria and migraine. *Am. J. Med. Sci.* 177:348–371.

Marine, D., Baumann, E. J., Webster, B. & Cipra, A. 1930. Effect of drying in air on the goitre-producing substance in cabbage. *Proc. Soc. Exp. Biol. & Med.* 27:1025–1026.

Martin, L. 1939. Autonomic imbalance and borderline states in thyrotoxicosis. *Proc. Roy. Soc. Med.* 32:1424–1429.

Mason, V. R., Courville, C. B. & Ziskind, E. 1933. The porphyrins in human disease. *Medicine* 12:355–439. Figs. 23.

Maurer, L. E. 1941. Niemann-Pick's disease. *Rocky Mountain Med. J.* 38:460–464.

May, W. 1935. Antagonismus zwischen Jod und Fluor im Organismus. *Klin. Wochens.* 14:790–792.

Medes, Grace. 1932. A new error in tyrosine metabolism: tyrosinosis. *Biochem. J.* 26:917–940.

Merksamer, D. & Kramer, B. 1939. Niemann–Pick's disease. *J. Pediatr.* 14:51–56.

Meulengracht, E. 1933. Is sporadic goitre dependent upon genotypical factors? *Endocrinology* 17:384–392.

Miller, R. & Perkins, H. 1920. Congenital steatorrhoea. *Quart. J. Med.* 14:1–9.

Milligan, E. H. M. 1926. Goitre in childhood. *Brit. Med. J.* ii. 373–376.

Mills, C. A. 1930. Diabetes mellitus: is climate a responsible factor in the etiology? *Arch. Int. Med.* 46:569–581.

Mills, Wesley. 1885. Ueber die Ausscheidung der Oxalsäure durch den Harn. *Virchow's Arch.* 99:305–313.

Mogensen, E. 1937. Three cases of idiopathic steatorrhoea (Gee-Thaysen's disease). *Quart. J. Med.* 30:119–141.

Moore, Henry, *et al.* 1936. The Gee-Thaysen disease, idiopathic steatorrhoea of adults and adolescents in non-tropical countries. *Quart. J. Med.* 29:481–516. Pls. 2.

Moss, R. E. & Walker, B. S. 1942. Pentosuria and diabetes mellitus. *J. Am. Med. Assn.* 120:25–26.

Müller, C. 1939. Angina pectoris in hereditary xanthomatosis. *Arch. Int. Med.* 64:647–700. Figs. 19.

Nesbitt, S. 1944. Acute porphyria. *J. Am. Med. Assn.* 124:286–294.

O'Donovan, D. K., McGrath, J. & Boland, S. J. 1942. Giardial infestation with steatorrhoea. *Lancet* 243:4–6. Figs. 2.

Osler, W. 1904. Ochronosis. *Lancet* i. 10–11.

Parmelee, A. H. 1932. Lipodystrophy, a report of six cases in children. *J. Am. Med. Assn.* 98:548–552. Figs. 6.

Pasqualini, R. Q. & Avogadro, A. 1942. Accion de la pitresina sobre la sed en la diabetes insipida. *Revista Soc. Argentina de Biol.* 18:88–92.

Patch, F. S. 1934. Cystinuria and cystine lithiasis. *Canad. Med. Assn. J.* 31:250–255. Figs. 5.

Pfaundler, M. v. 1924. Über die Entstehungsbedingungen von endemischem Kropf und Kretinismus. *Jahrb. Kinderhlk.* 105:223–276.

Pflüger, H. 1937. Die geographische Verbreitung des Kropfes in Europa. *Deut. Arch. Klin. Med.* 180:212–232. Figs. 3.

Pick, L. 1933. Niemann-Pick's disease and other forms of so-called xanthomatosis. *Am. J. Med. Sci.* 185:601–616. Figs. 12.

Pierce, S. J. S. 1934. A case of cystinuria. *Can. Med. Assn. J.* 31:182–184. Figs. 2.

Pieter, H. 1925. Une famille d'alcaptonuriques. *Presse Méd. (Paris)* 33:1310.

Pincus, G. & White, P. 1933. On the inheritance of diabetes mellitus. I. An analysis of 675 family histories. *Am. J. Med. Sci.* 186:1–14.

——— ———. 1934. II. Further analysis of family histories. *Am. J. Med. Sci.* 188:159–168.

——— ———. 1934. On the inheritance of diabetes mellitus. III. *Am. J. Med. Sci.* 188:782–790.

Plattner, W. 1938. Grössen- und Formverhältnisse der Kretinen hand. *Arch. J. Klaus-Stift.* 13:699–783. Figs. 11.

———. 1940. Die Kretinennase. *Arch. J. Klaus-Stift.* 15:195–258. Pls. 5, Figs. 10.

Pochin, E. E. 1944. Exophthalmos in guinea pigs injected with pituitary extracts. *Clin. Sci.* 5:75–91.

Pomeranz, M. M., Friedman, L. J. & Tunick, I. S. 1941. Roentgen findings in alkaptonuric ochronosis. *Radiology* 37:295–303. Figs. 7.

Prissmann, J. 1929. Stammbaum einer Familie mit Basedowscher Krankheit. *Arch. Rass. Ges.-Biol.* 22:205.

de Quervain, F. & Wegelin, C. 1936. *Der endemische Kretinismus.* Berlin. Pp. 206, figs. 120.

Radaeli, F. 1911. Contributo alla conoscenza dell' hydroa vacciniforme di Bazin. *Gior. Ital. Derm. e Sif.* 52:93–109. Figs. 4.

Read, J. 1939. Studies in exophthalmic goitre. I. Its incidence throughout the United States. *Arch. Int. Med.* 63:71–79.

Reich, S. 1934. Xanthomatosis and the Schüller-Christian syndrome. *Can. Med. Assn. J.* 31:256–265. Figs. 3.

Reiss, O. & Kato, R. 1932. Gaucher's disease. A clinical study with special reference to the roentgenography of bones. *Am. J. Dis. Child.* 43:365–386. Figs. 8.

Reveno, W. S. 1931. The cause of exophthalmic goitre. *Arch. Int. Med.* 48:592–597.

Rhind, E. G. G. & Wilson, A. 1941. Diabetes mellitus in Addison's disease. *Lancet* 241:37–39.

Richter, C. P. 1930. Experimental diabetes insipidus. *Brain* 53:76–85.

Riddle, O. 1929. The inheritance of thyroid size and the establishment of thyroid races in ring doves. *Amer. Nat.* 63:385–409.

Riebold, G. 1915. Die Erblichkeit der Struma. *Zeits. f. Abst. u. Vererb.* 14:1–11. Figs. 9.

Rimington, C. 1939. Porphyrins and their relation to the metabolism of blood pigments. *Proc. Roy. Soc. Med.* 32:1268–1275.

Robson, W. 1929. Protein metabolism in cystinuria. *Biochem. J.* 23:138–148. Figs. 2.

Rothstein, J. L. & Welt, S. 1941. Infantile amaurotic family idiocy. *Am. J. Dis. Child.* 62:801–843. Figs. 7.

Rowland, R. S. 1928. Xanthomatosis and the reticulo-endothelial system. *Arch. Int. Med.* 42:611–674. Figs. 11.

Rüdin, E. 1932. Ueber Ursachen des endemischen Kropfes und Kretinismus. *Münch. Med. Wochens.* 79:988–993.

Rundle, F. F. 1941. A study of the pathogenesis of thyrotoxicosis. *Lancet* 241:149–152. Figs. 7.

Rundle, F. F. & Pochin, E. E. 1944. The orbital tissues in thyrotoxicosis. *Clin. Sci.* 5:51–74.

Rundle, F. F. & Wilson, C. W. 1944. Ophthalmoplegia in Graves' disease. *Clin. Sci.* 5:17–29.

Rush, H. P. & Jones, L. T. 1925. The distribution of goitre among Indians. *Endocrinol.* 9:372–382.

Russell, D. S. & Barrie, H. J. 1936. Storage of cystine in the reticulo-endothelial system and its association with chronic nephritis and renal rickets. *Lancet* 231:899–905. Figs. 6.

Salkowski, E. & Jastrowitz, M. 1892. Ueber eine bisher nicht beobachtete Zuckerart. *Contlbl. f. Med. Wissens.* 30:337–339.

Sawin, P. B. & Glick, D. 1943. Atropinesterase, a genetically determined enzyme in the rabbit. *Proc. Nat. Acad. Sci.* 29:55–59.

Schmid, M. 1940. Die Beziehungen der Schilddrüse zu Alter, Geschlecht und Konstitution. *Zeits. f. Konst-lehre* 24:313–336. Figs. 16.

Schmidt, C. R. & Hertzler, A. E. 1942. Cardiotoxic goitre — a distinct entity. *Endocrinology* 31:684–688.

Sheldon, J. H. 1934. Haemochromatosis. *Lancet* 227:1031–1036.

———. 1935. *Haemochromatosis.* Oxford Press. Pp. 382.

Shelton, E. K. 1931. Familial hypothyroidism. *Endocrinology* 15:297–306. Figs. 7.

Shillington, M. A. 1945. Congenital exophthalmos. *J. Am. Med. Assn.* 129:583.

Siemens, H. W. 1922. Hydroa vacciniforme. *Arch. f. Derm. u. Syph.* 140:314–324.

Silva, J. Ramos e. 1943. Lipid proteinosis (Urbach-Wiethe). *Arch. of Derm. & Syph.* 47:301–326. Figs. 8.

Silver, S. & Reiner, M. 1934. Essential fructosuria. *Arch. Int. Med.* 54:412–426.

Simons, A. 1911. Crampi bei amyotrophischer Lateralsklerose. *Zeits. f. Neurol. u. Psychiat.* 15:23–28.

———. 1913. Lipodystrophia progressiva. *Zeits. f. Neurol. u. Psychiat.* 5:29–38. Figs. 4. 19:377–397. Pls. 3.

Smelser, G. K. 1937. A comparative study of experimental and clinical exophthalmos. *Amer. J. Ophth.* 20:1189–1203. Figs. 18.

———. 1939. The histology of orbital and other fat tissue deposits in animals with experimentally produced exophthalmos. *Amer. J. Pathol.* 15:341–351. Pls. 2.

———. 1943. Water and fat content of orbital tissues of guinea pigs with experimental exophthalmos produced by extracts of the anterior pituitary gland. *Amer. J. Physiol.* 140:308–315.

Smith, E. B. & O'Flynn, E. 1933. Familial hepatomegaly of uncertain pathology. *Lancet* 224:297–299. Figs. 2.

Smith, H. 1930. Progressive lipodystrophy of the lower extremities. *Amer. J. Med. Sci.* 179:758–760. Fig. 1.

Smyth, C. J. & Freyberg, R. H. 1940. A study of the hereditary nature of gout. *Univ. Hosp. Ann Arbor* 6:62–63.

Snapper, I. & Parisel, Ch. 1933. Xanthomatosis generalisata ossium. *Quart. J. Med.* 26:407–417. Pls. 4.

Soecknick, A. & Thoenes, F. 1927. Über familiäre Pankreasinsuffizienz, ein Beitrag zur Pankreaspathologie des frühen Kindesalters. *Jahrb. f. Kinderhlk.* 115:315–331.

Soskin, S. 1941. The blood sugar: its origin, regulation and utilization. *Physiol. Rev.* 21:140–193.

Spellberg, M. A. & Leff, W. A. 1945. The incidence of diabetes mellitus and glycosuria in inductees. *J. Am. Med. Assn.* 129:246–250.

Srb, A. M. & Horowitz, N. H. 1944. The ornithine cycle in Neurospora and its genetic control. *J. Biol. Chem.* 154:129–139.

Spix, J. B. & Martius, C. F. P. 1824. *Travels in Brazil.* London. Vol. I. Pp. 298.

Stecher, R. M. & Hersh, A. H. 1945. The inheritance of human gout or the incidence of familial hyperuricemia. *Genetics* 30:24.

Steensma, F. A. 1914. Familiäre orthostatische Urobilinurie. *Neerl. Tijdskr. v. Geneesk.* 58: Part I, 248–251.

Steiner, F. 1936. Beobachtungen zur Erblichkeit der Basedowschen Krankheit, des Biedl-Lawrenceschen Syndroms und der Cholelithiasis. *Zeits. f. Konst-lehre* 20:73–77.

Steiniger, G. 1939. Zur Genetic des Diabetes mellitus. *Zeits. f. Menschl. Vererb. Konst.* 24:27–45.

Stocks, Percy. 1928. Goitre in the English school child. *Quart. J. Med.* 21:223–275. Figs. 4.

Stocks, Percy & Karn, Mary N. 1927. On the relation between the prevalence of thyroid enlargement in children and mortality from cancer and other diseases. *Ann. of Eugen.* 2:395–404.

Sutphin, A., Albright, F. & McCune, D. J. 1943. Five cases (three in siblings) of idiopathic hypoparathyroidism associated with moniliasis. *J. Clin. Endocrinol.* 3:625–634. Figs. 2.

Talbott, J. H. 1940. Serum urate in relatives of gouty patients. *J. Clin. Investig.* 19:645–648.

Tallerman, K. H. 1936. Lipodystrophia progressiva. *Proc. Roy. Soc. Med.* 29:749–750.

Tatum, E. L., Bonner, D. & Beadle, G. W. 1944. Anthranilic acid and the biosynthesis of indole and tryptophan by Neurospora. *Arch. Biochem.* 3:477–478.

Thannhauser, S. J. 1929. Lipidoses: diseases of the cellular lipid metabolism. *Oxford Medicine.* 4:214 (3–365). Figs. 78.

———. 1941. *Lipidoses: Diseases of the Cellular Lipid Metabolism.* Oxford Press. Pp. 370.

Thaysen, Th. E. H. 1935. Ten cases of idiopathic steatorrhoea. *Quart. J. Med.* 28:359–395. Pl. 1.

Thin, R. 1929. Familial cystinuria. *Edinb. Med. J.* 46:490–492.

Toenniessen, E. 1922. Über die Vererbung der Alkaptonurie des Menschen. *Zeits. f. Abst. u. Vererb.* 29:26–30.

Török, L. 1893. De la nature des xanthomes. *Ann. de Derm. et Syph.* 4:1109–1156, 1261–1273.

Trimble, H. C. & Keeler, C. E. 1938. The inheritance of "high uric acid excretion" in dogs. *J. Hered.* 29:281–289. Figs. 4.

Turner, W. J. 1938. Acute idiopathic porphyria. *Arch. Int. Med.* 61:762–773.

Tyrer, J. 1943. A case of infantilism with goitre, diabetes mellitus, mental defect and bilateral primary optic atrophy. *Med. J. Australia.* ii. 398–401. Figs. 3.

Unterrichter, Leo v. 1938. Endemischer Kropf und Missbildung. *Zeits. f. Mensch. Vererb. u. Konst.* 22:160–164. Figs. 5.

Virchow, R. 1866. Ein Fall von allgemeiner Ochronose der Knorpel und knorpelähnlichen Teile. *Virchow's Arch.* 37:212–219. Pl. 1.

Waldenström, J. 1937. Studien über Porphyrie. *Acta Med. Scand.* Suppt 82, pp. 254.

Warner, E. C. 1933. A case of hepatomegaly due to von Gierke's disease. *Lancet* 224:1070–1071. Figs. 2.

Watson, W. N. B. & Ritchie, W. T. 1925. Progressive lipodystrophy. *Quart. J. Med.* 18:224–239. Pls. 2.

Weber, F. P. 1931. A glycosuric family without hyperglycaemia. *Lancet* 221:71–72.

Weil, A. 1884. Ueber die hereditäre Form des Diabetes insipidus. *Virchow's Archiv.* 95:70–95.

Weil, A., Jr. 1908. Ueber die hereditäre Form des Diabetes insipidus. *Deut. Arch. f. Klin. Med.* 93:180–200.

Wilgus, H. S., Jr., Gassner, F. X., Patton, A. R. & Gustavson, R. G. 1941. The goitrogenicity of soybeans. *J. of Nutrition* 22:43–52.

Wilson, D. C. 1939. Distribution of fluorosis in India and in England. *Nature* 144:155. Fig. 1.

———. 1941. Fluorine in the aetiology of endemic goitre. *Lancet* 240:211–212.

Winkelman, N. W. & Eckel, J. L. 1925. Adiposis dolorosa (Dercum's disease). *J. Am. Med. Assn.* 85:1935–1939. Figs. 6.

Wright, I. S. 1931. Hereditary and familial diabetes mellitus. *Am. J. Med. Sci.* 182:484–497.

Young, F. G. 1941. "Growth" and the diabetogenic action of anterior pituitary preparations. *Brit. Med. J.* ii. 897–901.

Zehnder, E. 1937. Zur Kenntnis der Somatologie des endemischen Kretinismus. *Arch. J. Klaus-Stift.* 12:273–420. Many figs.

Chapter XIV

HEMOPHILIA AND RELATED HEREDITARY CONDITIONS

AMONG abnormalities of the blood system *hemophilia* takes a leading place. It was first characterised by John C. Otto in Philadelphia in 1803, but as early as 1519 Albucasis in Cordova described men who bled to death when not severely wounded. From statements in the Talmud (second century A.D.) regarding circumcision it is evident that there were hemophilics in ancient Jewish families. There was also some knowledge of its "sex linkage" (see M. Fischer, 1932). Fordyce (1784) pointed out the hereditary nature of this abnormality and described a female hemophilic. Wickham Legg (1872), in a treatise on hemophilia, found "that women are much less disposed than men, the attacks being milder and atypical." This view nearly corresponds with recent knowledge of the subject.

The recent evidence, as summarized in this chapter, necessitates a fundamental revision of current views, as it shows (1) that heterozygous females not very infrequently are partial bleeders, the bleeding appearing in some cases only before puberty or after the menopause, (2) that hemophilia, while generally sex-linked, is (like other abnormalities) dominant in occasional families and probably recessive in rare cases. It is recessive in pigs (but see p. 610). Sex-linkage should therefore not be regarded as an essential diagnostic feature of hemophilia, although this is its usual method of inheritance. Several other types of bleeders are now known, including a dominant sex-linked form in which females are severely affected, as well as dominant pedigrees of epistaxis (nosebleed), telangiectasis and capillary fragility. It is possible that prolonged clotting time has been overemphasized as an essential diagnostic feature of hemophilia. It is clear that many different genes exist which produce bleeders of different types, some of these genes being sex-linked and some dominant. Genes producing mild forms of bleeding appear to be particularly common in Russia. Finally, it is highly probable that homozygous female hemophilics exist; and in any case severe bleeding from slight wounds is certainly not incompatible with the female sex, as has frequently been assumed in the past.

Otto (1803) explained that hemophilia was confined to males; he called them *bleeders* and pointed out that although females were exempt they could transmit the condition to their male children. Hemophilia is a typical example of recessive sex-linked inheritance and a large number of extensive pedigrees have now been published, generally following this rule with minor deviations. Hay (1813) published the first extensive pedigree of hemophilia (Fig. 210), in which the condition was followed through six generations in the Appleton-Swaine family.

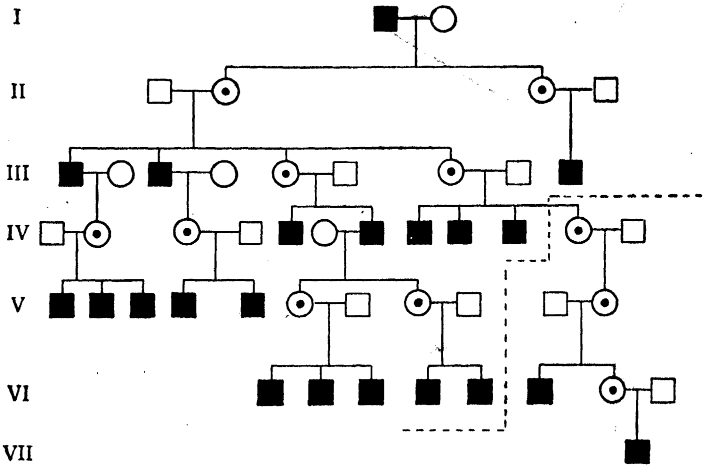

Fig. 210. Hay's original pedigree of hemophilia. The part below the dotted line was added by Osler.

Case I. 1 lived at Ipswich, Massachusetts, about 1713 and died in old age from hemorrhage where the skin was worn from his hips by long confinement in bed. His two daughters both transmitted the condition to their sons. Two of these sons again transmitted to their grandsons, and two of the five daughters in generation III again passed it on to their sons. In 1885, Osler extended this pedigree, adding the part below the dotted line in Fig. 210. He states that VII. 1 died *ca.* 1873 and that the condition was handed down to the seventh generation in about two hundred years. It will be seen that four affected males have transmitted the condition to their thirteen grandsons and that in one line it has been transmitted through five successive generations of normal females. Nissé (1927) has endeavoured to minimize the evidence for transmission by males, but even he is forced to admit its occurrence in the case of IV. 5 and IV. 7. He contributes a fresh pedigree which also follows Nasse's Law, i.e., the course of the X-chromosome (see Fig. 4, p. 11).

Nasse (1820) formulated the law: women transmit the condition from fathers to their children, but never exhibit it. This conclusion could only have been derived from a study of Hay's pedigree. He refers to the work of Otto, Hay and Fordyce. There are many subsequent proven instances of transmission by an affected father to his grandsons through his normal daughters, all of whom will be potential transmitters since they all receive his X-chromosome.

In many pedigrees, especially of the more extreme forms of hemophilia, however, the mortality of affected males is so high that few or none survive to the reproductive age. This led Lossen (1876) to formulate his "law," based on a study of the Mampel family in Heidelberg, that no son, even though a bleeder, ever transmits. Modern work has shown this to be quite erroneous, resulting simply from the sublethal condition of hemophilic males. In the Mampel family he described, nine out of seventeen cases bled to death.

In recent years the extensive literature of hemophilia has been devoted mainly to (1) the etiology and possible "cure" of the disease, (2) its relation to other forms of bleeding, (3) the occurrence of hemophilia in women. These topics will be considered, following a survey of the earlier work. The records indicate that hemophilia is particularly frequent among the Germanic peoples. If **h** represents the gene for hemophilia and **H** its normal allelomorph, then men will be **H** or **h** and women **HH, Hh** or (if viable) **hh.** From the later records it will be clear that the hemophilia in some families is consistently more severe than in others, and there are certain other family differences in the blood picture, indicating the existence of perhaps several different genes for hemophilic conditions — all probably alleles. As Haldane (1935) points out, the severe form, i.e., the wide mutation, is much more frequent than the mild form, and this is in accord with the mutation rates for wide and narrow mutations found in some other organisms. Haldane pointed out that in a population containing a sublethal gene such as hemophilia in the X-chromosome, about one-third of the chromosomes with such a gene will be carried by males and most of these will be lost in each generation. The mutation rate to renew the gene must then be approximately equal to the frequency of hemophilia, which he estimated at 1 in 50,000 in the population of London.

That such mutations occur, there is plenty of evidence. Since hemophilia is known to have been transmitted through as many as five successive generations of normal females, the evidence for a fresh mutation will be stronger the larger the number of normal males in the female line of ancestry. From this point of view the pedigree of

Boggs (1934) is most striking (Fig. 211). It stretches back five generations with large numbers of normal males, making it certain that hemophilia was not inherited through the females. The only possible loophole is that IV. 11 might have been an illegitimate child with a hemophilic father. Considering the rarity of hemophilic fathers, this possibility can be dismissed. Boggs lists fourteen other cases of "spontaneous" hemophilia (mutations) from the literature. Another strong case is that of DeLacey (1931). Figure 212 shows that III. 2 could hardly have been a carrier, as none of her five sons nor the seven sons of her two daughters showed the condition. The male twins in generation five were presumably not monozygotic, but the point is not mentioned. The condition must then have arisen in the germplasm of IV. 9, or from a mutated germ cell of her father, III. 1.

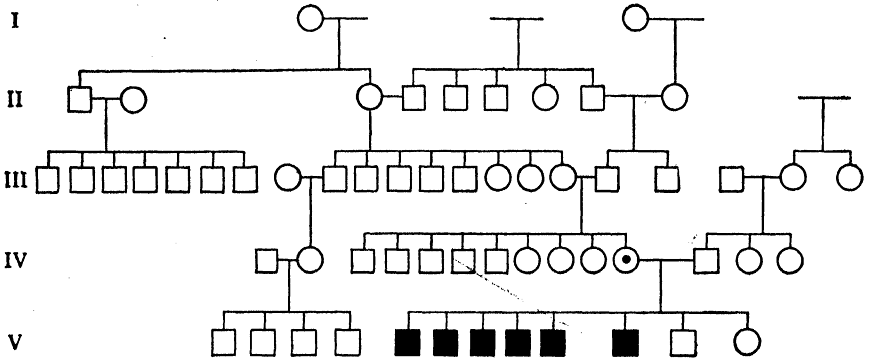

Fig. 211. Mutational origin of hemophilia. (After Boggs)

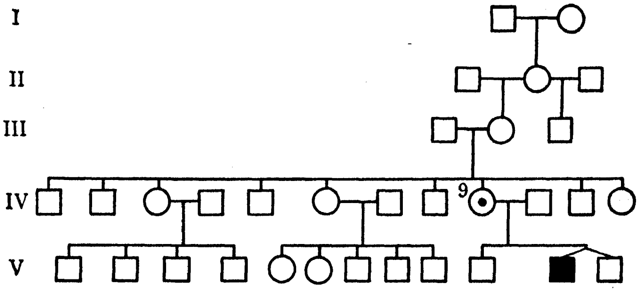

Fig. 212. Mutational origin of hemophilia. (After DeLacey)

In still another case (Rewcastle, 1939) the evidence for mutation is less strong (Fig. 213). He estimates that

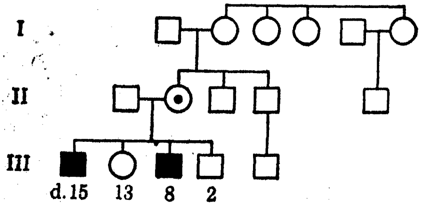

Fig. 213. Possible origin of hemophilia by mutation. (After Rewcastle)

such a pedigree could occur through inheritance *ca.* once in twenty-one times and considers that at least half of all such affected sibships show no family history. Price Thomas (1931) described a boy with prolonged clotting time, but no case of hemophilia in the ancestry for three generations. He had hemarthrosis and profuse hemorrhages, but the blood-calcium was low whereas in hemophilia it tends to be high. In the discussion, Dr. Wyllie mentioned a case in which there was no trace in the family history for seven generations. In these cases, since the normal females transmit, it is their ancestry rather than that of the fathers, that needs to be traced.

Sirks (1937) has put forward the theory that nearly all males carry a recessive gene **h** for hemophilia in the Y-chromosome and that the *de novo* appearance of hemophilia does not signify a mutation but merely crossing-over of this gene from the Y- to the X-chromosome. Such crossing-over is known to happen in Lebistes and other fishes and in various cases cited in this book. How the Y-chromosome acquired this hidden supply of defective **h** genes is not explained, but a cross-over rate of *ca.* 0.5 per cent is assumed. On this theory the male genotypes will be $\frac{\mathbf{XH}}{\mathbf{YH}}$, $\frac{\mathbf{XH}}{\mathbf{Yh}}$, $\frac{\mathbf{Xh}}{\mathbf{YH}}$ and $\frac{\mathbf{Xh}}{\mathbf{Yh}}$, the last only being hemophilic. The female genotypes are $\frac{\mathbf{XH}}{\mathbf{XH}}$, $\frac{\mathbf{XH}}{\mathbf{Xh}}$ and $\frac{\mathbf{Xh}}{\mathbf{Xh}}$, the last being possibly lethal in some cases. Haldane (1938b) has pointed out difficulties with this ingenious hypothesis which make it highly improbable. He shows that this emptying of defective hemophilic genes from the Y into the X by crossing-over cannot have been going on for as long as 1,000 generations and the cross-over rate must have formerly been very much less. Moreover, there must be some **YH** chromosomes (resulting from the assumed crossing-over). From the mating $\frac{\mathbf{XH}}{\mathbf{Xh}}$ ♀ × $\frac{\mathbf{XH}}{\mathbf{YH}}$ ♂ half the sons would be $\frac{\mathbf{Xh}}{\mathbf{YH}}$ and these normal males must transmit hemophilia to their daughters' sons. It may be pointed out that such a case is stated (Dunn, 1883) to have occurred, a normal son with three brothers who were bleeders having transmitted hemophilia through his son to two of seven grandsons. Again, on this hypothesis, mild hemophilia (**h′**) should occasionally occur in one fraternity of a pedigree showing severe hemophilia, but hitherto the conditions appear to be uniform in each pedigree. Dunn recorded eleven families, in some of which the condition was clearly sex-linked. In one, three daughters bled to death from epistaxis and the mother developed purpura.

Haldane (1938a) and Gun (1938) have traced the hemophilia in the royal families of Europe. There is no trace of the condition in the present British royal family, but Haldane thinks that it originated as a mutation in Queen Victoria. It seems more probable that the actual mutation, whatever its nature, occurred in a germ cell of her father, the Duke of Kent. Gun suggests that her mother, the Duchess of Kent, might have transmitted it, but she was one of ten normal children (five sons and five daughters) and there is no hemophilia in her other descendants.

By an analysis of the pedigrees collected by Birch (1937), in which there are records of twenty-one daughters of hemophilic fathers who in turn had one or more affected sons, Haldane and Philip (1939) are able to show (1) that the daughters of hemophilic men produce equal numbers of normal and hemophilic sons, (2) that half the sisters of hemophilic men are heterozygous for hemophilia. Haldane's (1935) calculations indicate that a hemophilic gene will die out, on the average, in about three generations in a stable population, but in some families it persists through many generations.

Fairbank (1930) gives a pedigree of typical hemophilia with ten cases (all males) in three generations. The condition can be traced back for six generations. The bleeding is frequently into the knee-joint but in one case is mainly epistaxis (nosebleed). In another family (Mills, 1930) with twelve or fourteen cases (males) in four generations, five daughters of a hemophilic all transmitted to their sons. The sibships showed 10 affected : 10 normal males. In a family with four affected sons of two normal mothers who were sisters (Seddon, 1929), two died and the third developed hematomyelia (bleeding into the spinal cord) following an accident. Fonio (1933) described a Swiss pedigree of hemophilia with seven cases in two generations at Soglio where there is much inbreeding. The symptoms included bleeding into elbows, knees and foot joints. The previous generations were normal so far as traced, so this case might have had a mutational origin or it might be connected with the Tenna family in the same canton. Muir's (1906) South African Dutch family of severe hemophilics included three cases of Nasse transmission in five generations. There were at least twenty-seven hemophilics in seven generations, descended from a man who was born in 1783 and died of epistaxis in 1852.

Enriques (1922) cites a family with hemophilia in mother, daughter and granddaughter only (supposed hologynic inheritance) but there are no clinical details. It may be pointed out that Enriques introduced the terms holandric and hologynic in this paper. He also cites a pedigree of Grandidier with "hemophilia" in the mother and three daughters.

A strange case of "acquired hemophilia" is described by Brainbridge (1937). An English architect in Nairobi, Kenya, age forty-one, had his appendix removed ten years previously without untoward effect but bled to death following tonsillectomy. There was no hemophilia in his ancestry.

The criteria of hemophilia as listed by Joules and Macfarlane (1938) are (1) a tendency from infancy to excessive bleeding from trivial injuries, (2) later, hemorrhage into the joints, (3) delay in coagulation but no quantitative change in platelets, prothrombin, fibrinogen or calcium content, (4) absence of any cause for hemorrhagic tendency except defective blood coagulation. Retardation of coagulation also occurs in prothrombinopenia, fibrinogenopenia, heparinopenia and extreme thrombocytopenia. Hemophilic blood, like that of lower vertebrates and of embryos, remains stable at room temperature, but clots at a temperature of 30° to 45° C. Pickering and Gladstone (1924) therefore suggest that hemophilic blood is in an embryonic condition.

Witts (1941) has compared critically the various hemorrhagic conditions and emphasizes the part played by the capillaries. They contract well in hemophilia and the bleeding time is normal, but when they relax following a wound hemorrhage recurs from failure of coagulation. Thromboplastin is found to consist of a water-soluble heat-labile protein and a fat-soluble heat-stable liquid. Witts suggests that hemophilia is associated with shortage of the water-soluble factor and purpura hemorrhagica with shortage of the fat-soluble factor.

It appears to be established that splenectomy effects a permanent cure of *purpura hemorrhagica*, but the reasons are obscure. That the symptoms can be removed, renders the disease more serious than before from a eugenic point of view, since the transmission to the next generation remains, of course, unaffected. In an earlier paper, Witts (1932) reported that Osler's telangiectasis is little rarer at Guy's Hospital than hemophilia. It is distinguished by the blood being normal. Hess (1916) recognized the diminished number of platelets in purpura hemorrhagica. When they are reduced to 50,000 per cubic millimeter from any cause there is excessive bruising and bleeding from trivial injuries. The bleeding time is prolonged and the tourniquet produces "purpuric eruption."[1] Witts (1932) published three pedigrees: 1. Five cases (4♂ 1♀) in two generations; probably dominant. 2. Two boys and a girl in a family with normal parents and two normal sibs. This is either recessive or an irregular dominant. 3. Four children from normal parents died of hemorrhage from the cord at birth. Of eleven children, all but the eldest suffered from hemorrhage of the cord. This points to some placental effect like that in erythroblastosis foetalis (*q.v.*), or lack of vitamin K.

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[1] Copley and Lalich (1942b) have introduced a new test for hemostasis, which they call *clot resistance.* This is lower than normal in hemophilics, but injection of extract of *Bursa pastoris* following blood transfusion increased the clot resistance in two cases.

Witts recognized only three types of bleeders: (*a*) hemophilia, (*b*) telangiectasis, (*c*) the hereditary hemorrhagic diathesis. The latter has symptoms of purpura hemorrhagica but with the platelets inconstant, and the frequency is about twice as high in women as in men. Willebrand's type of sex-linked dominant bleeding (see below) appears, however, to be distinct from this. There are other types as well which apparently fall outside his classification.

Hemophilia is common in the Black Forest, in mountain valleys and small isolated villages. Schloessmann (1924–1925) studied 24 families (1596 persons), following some of them through six or seven generations. The largest pedigrees are the Kiefer (298) and Bott (219) families, which are interrelated and make a complex of 517 individuals. The next largest are Hössli's (about 400) and Lossen's (Mampel) family with 213. Five cases of "sporadic" hemophilia are cited. In one the pedigree includes large families in two generations with a single hemophilic, giving strong evidence of a *de novo* origin. In another large pedigree in six generations it appears in two brothers of the fifth generation. In this case the germinal origin would have been in the mother. She had ten brothers, all normal, so her mother could scarcely have been a transmitter. In another pedigree three brothers in the third generation are bleeders. Their mother's mother, who should have been a carrier, had five healthy brothers, some of whom should have shown the condition if it was in the germplasm of this family. But the mother of the three brothers had strong nosebleed as a girl, and one of their sisters bled abnormally from the skin and under the skin from slight scratches. So she was probably heterozygous, the mutation having occurred in the germ cells of her father. In another case the mother of two bleeders bled unusually copiously in menstruation and at childbirth. This is characteristic of some women carriers, and Schloessmann believes that women carriers can be detected by the coagulation time.

That bleeder males can transmit, is now proven by many cases besides those in Hay's original pedigree (Fig. 210). Pedigree XIX of Schloessmann contains a case of a hemophilic father transmitting it to his daughter's son. In the Kiefer pedigree, a bleeder born in 1798 married twice, and by each wife transmitted hemophilia through the daughters to later generations. One at least of the female descendants of this family bled from the nose and teeth, showed blue marks under the skin and had a slow clotting time. Female "bleeders" only occur in the Calmbach complex of families, yet the women in other pedigrees frequently show such a tendency, and every carrier tested was found to have an increased coagulation time. Nevertheless, the complete phenomena of hemophilia do not generally show in women. Since all the X-bearing sperm of a male bleeder will carry the defective X-chromosome, it is obvious that if he has any female children they must all be transmitters. Non-viability of the X-bearing sperm would prevent such transmission, but hemophilic adult males who marry have both male and female children. On the other hand, they cannot normally transmit to a son, because a son does not get an X-chromosome from his father.

Bulloch and Fildes (1910), in their extensive monograph on hemophilia, bring together a vast amount of information and many pedigrees, with a full consideration of the early literature. In the 44 families studied there were 644 males and 464 females — a great excess of males. The marriage-rate of males in bleeder families is very much lower than of females (9.6 per cent : 36.8 per cent). Little and Gibbons (1921) explained the large excess of hemophilic to normal males in sibships of hemophilic families by assuming the presence of a lethal factor linked to the normal allele of hemophilia. Thus they found 551 hemophilic males where 457 were expected. If a linked lethal is present, there should also be a decrease of female children in certain sibships. The sex-ratio was found to rise correspondingly from 122.55 to 157.8. Similar but less marked sex-ratios were found with color blindness. Catcheside and Lea have recently made important studies of the dominant and recessive lethal mutations in Drosophila (*J. Genetics*, Vol. 47, No. 1, 1945).

Bauer and Wehefritz (1924) gave a number of pedigrees of hemophilia and *thrombopenia* (a deficiency of thrombocytes in the blood). The latter is a simple dominant, appearing in either sex in all generations, and needs to be carefully distinguished clinically from true hemophilia. Some supposed female "bleeders" are cases of thrombopenia.

Warde (1923) traced a pedigree of hemophilia with twelve cases in five generations (Fig. 214). The fifth generation contained seven normal daughters and seven sons, four of whom were hemophilic. The propositus (IV. 8), as a girl of ten, was found unconscious through loss of blood from a tooth extraction. Afterwards she had severe hemorrhage from a cut thumb, and on another occasion bled for two weeks after opening an abscess. She was easily bruised, and when her hemophilic son was born she suffered from hemorrhage. The son died from bleeding at the age of five years. The coagulation time of this woman was 3 to 3.35 minutes at 37° C. After special treatment she survived an operation for carcinoma of the breast, but the wound bled for three weeks. This woman no doubt had hemophilia in a reduced and sublethal form. Such cases show that irregular dominance in the female is just as characteristic of hemophilia as it is of color-blindness.

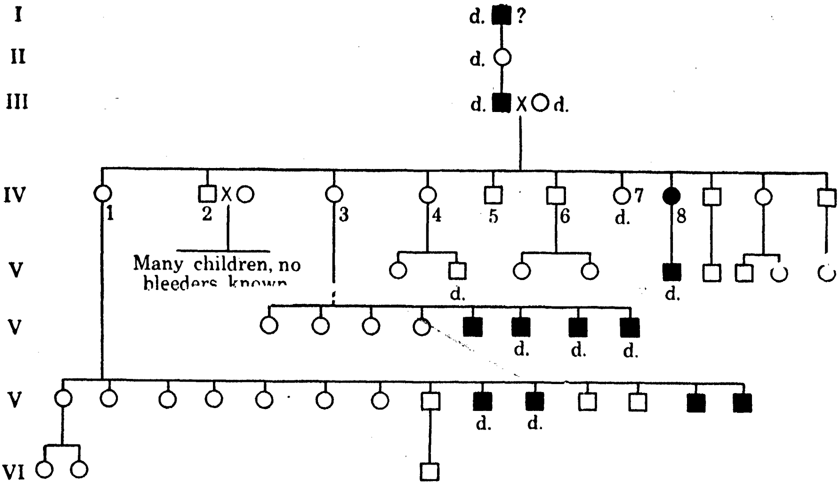
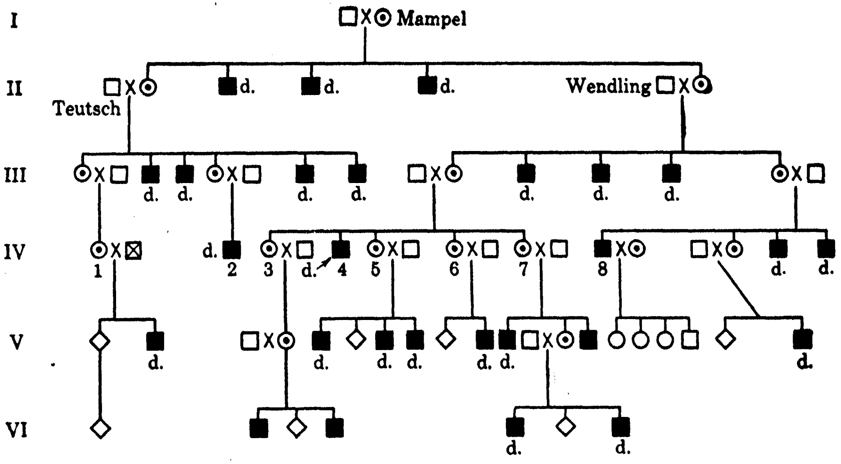


Fig. 214. Pedigree of hemophilia. (After Warde)

Weinberg (1924) suggested in 1912 that homozygous female bleeders (there can be no such thing as a homozygous male bleeder, because the male has only one X-chromosome) were non-viable. This, if true, would account for the absence of female bleeders showing the full symptoms. Little and Gibbons (1921) made the same suggestion, and Mohr (1926) reached the same conclusion from a study of the mortality in a group of cases. Nevertheless there is strong evidence for the existence of homozygous female bleeders (see below). B. Lloyd (1925) described an American family and a Russian family, each of four generations, in which bleeding is accompanied by swelling of the joints followed by discoloration and pain due to internal bleeding. The condition is incompletely recessive in heterozygous females, who show the symptoms, but less than males. One such woman who was a "pronounced bleeder" had a normal son, showing that she must have been heterozygous for the condition.

Klug (1926) has published an account of the sixth generation of the famous Mampel family. The Mampels themselves no longer exist in Kirchheim, the descendants having emigrated to America, where nothing further is known of them. But the Teutsch and Wendling families, descended respectively from Elizabeth Mampel (born 1821) and Anna K. Mampel (born 1830), have been followed in two pedigrees (see Fig. 215). Of the fifty-two families in this descent, only twelve have hemophilia, and in these only the males show abnormal bleeding phenomena. Klug points out mistakes of Lossen, whose scheme showed thirty-seven bleeders where there were really only twenty-three (including four in the younger generation). The others said they were bleeders in order to escape military service. The bleeding propensity is stronger in some branches of the family than in others. These pedigrees include but one true bleeder-father (IV. 8), who had three normal daughters and a normal son. But there is no doubt that these daughters would all be carriers. The modern families are smaller than formerly, and there is no excessive fertility.



⊠ = Pseudo bleeder

Fig. 215. Pedigree of the Mampel family, in part. (After Klug)

K. H. Bauer, from a study of 233 hemophilic pedigrees, including the Mampel family, also concluded that the homozygous female is lethal. Klug disagreed with this, but points out a discrepancy from expectation in that *all* the women in the Wendling family are carriers, and this can hardly be mere chance. But in the whole Mampel family there are 66 sons, of whom 27 are bleeders and 39 normal; and 58 daughters, of whom 14 are carriers and 10 not (as yet), the remainder not having had children.

An interesting pedigree of hemophilia in an American family is described by Davidson and McQuarrie (1925). Eight generations descended from the marriage of a Quaker woman named Jasper to Sir William Crispin in 1746 contain fourteen cases (Fig. 216). It has been handed down through normal female carriers for at least six generations to VIII. 5. Number V. 2 had frequent attacks of uncontrollable bleeding from nose and teeth, and was much crippled by joint hemorrhages. His "two sons and grandson" were not hemophilic, but according to the pedigree he had one son and a daughter. Again VI. 10 is stated to have had two sons and two daughters, all normal, yet the pedigree shows only two daughters. The descendants of normal males are all normal. Case VI. 12 is another one of a hemophilic with children, his four sons all being normal as expected. Evidently in this family the bleeding is not so severe as in the Mampel family, but in female

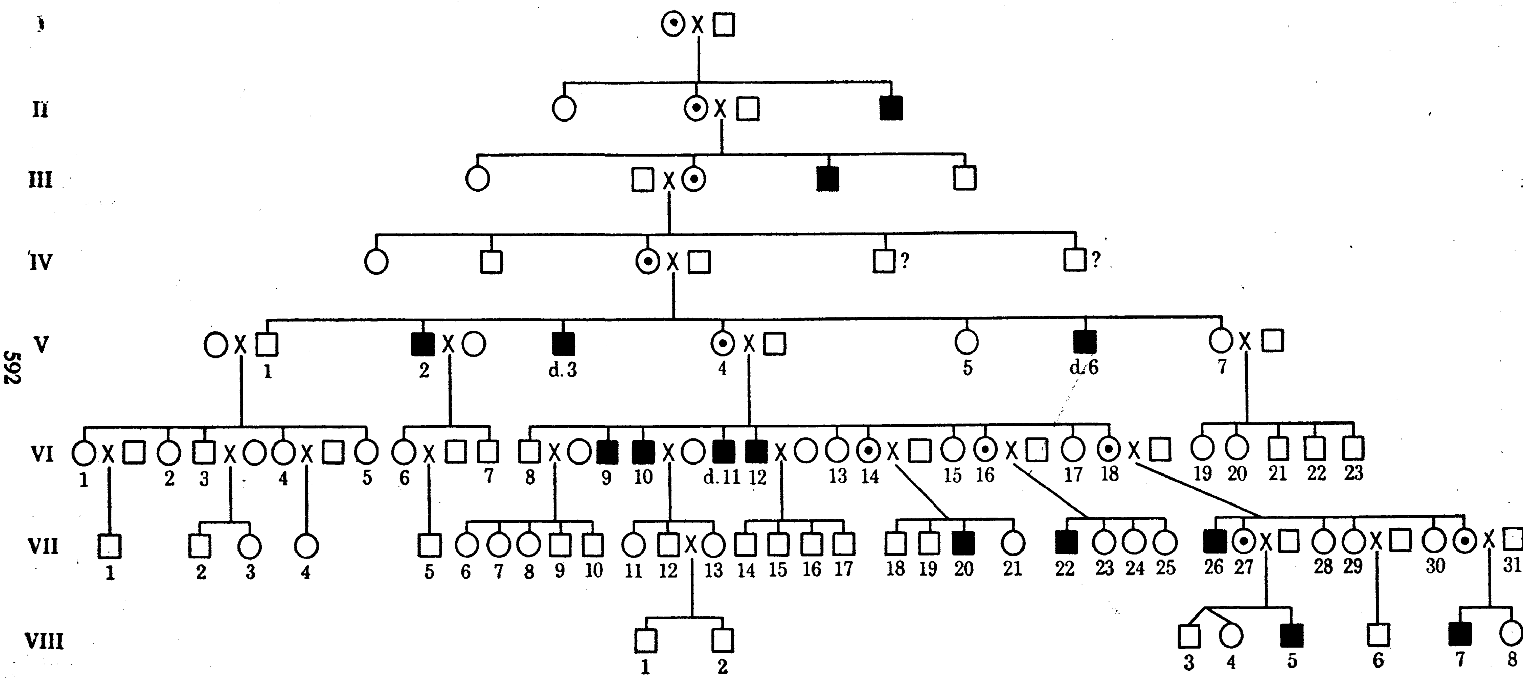


Fig. 216. Pedigree of hemophilia. (After Davidson and McQuarrie)

transmitters the coagulation time and prothrombin time were nevertheless greatly prolonged. Of the 27 sons of transmitters in this pedigree, 14 are bleeders, 11 normal and 2 doubtful. Of the 12 women who have married, 10 have transmitted the disease.

Davidson and McQuarrie also describe a sporadic case of hemophilia with the characteristic blood picture. His ancestors and collaterals (sixty-five individuals) showed no trace of the condition for four generations back.

Nissé (1927) examined the 75 pedigrees of Bulloch and Fildes and showed that 47 out of 524 bleeders left offspring. In twelve cases there was transmission through daughters to their children, but most bleeders fail to reach adult life. In three instances there was apparent transmission through a normal male, but Pickering (1928) points out that these were not true hemophilics. The speed of clotting was respectively 4½, 6½ and 9 minutes, and in one the count of platelets was only 87,000 per cubic millimeter of blood. The condition was therefore not hemophilia, but in one thrombocytopenic purpura is indicated.

Lukowski (1927) gives a pedigree showing eight cases of hemophilia in five generations of a wealthy and intelligent Polish family (Posmiak), extending over a period of 132 years (1791–1922). In this family the condition takes an extreme form. All the hemophilics died from slight accidents, and the gene is essentially a lethal. None of the women died of hemorrhage, but many developed bluish marks from a slight bruise. The descendants from a sister of a bleeder show no bleeders through five generations. A baby, V. 23, born in 1922, was lightly slapped at birth to resuscitate him, causing large bluish marks lasting a week. At the age of four he bled for forty-eight hours from a superficial chin wound, and later he died after forty-four hours' hemorrhage from a slight laceration of the rectal mucosa. A brother, after many bleedings from slight wounds, died at the age of four from nosebleed caused by bumping his nose.

Another pedigree of hemophilia involves several interesting features (Madlener, 1928). H. Dörr, II. 6 in the pedigree (Fig. 217), had seven children and died in 1866, at the age of forty-six, of a clot on the brain. One of his daughters was a carrier, and another (III. 6) had subcutaneous hemorrhages from an early age and often bled all day from a scratch. She became very pale from bleeding. Frau Dörr, her mother, had no known bleeders in her pedigree or relatives (forty-eight individuals included), so III. 6 must have been heterozygous for hemophilia. Cases II. 1, 4 and 6 were also red-green color blind, this condition being inherited like hemophilia. In this pedigree none of the female carriers showed longer clotting time, so that the condition in III. 6 is all the more striking. The women III. 10, IV. 4, IV. 6 and V. 1 all belonged to blood group A. The suggestion of Lenz that the case of III. 6 was perhaps one of pseudo-hermaphroditismus masculinus, an intersex, is very far-fetched.

The Calmbach bleeders, a well-known family in the Black Forest, were first studied by M. Fischer in 1889. Schloessmann (1930) made an extensive investigation of them from the church books. Studt (1937) has compiled a large pedigree dating from 1614 and containing four different kindreds, including two already known. It covers 11 generations and includes 85 bleeders (63♂ 22♀), 52 women are normal conductors, and 17 normal sons against 63 bleeders are recorded. The reason for this large excess of affected over normal men is not clear. There is a possible connection between this Württemberg family and the Swiss pedigree of Hoessly-Haerle (1931) referred to below. The Alemannen had their origin in the Black Forest and the Tenna and Safiens districts of Switzerland may have been populated by Germans from this area at the turn of the thirteenth century. Studt concludes that there is a *female hemophilia* which is distinguished from the male only quantitatively, the mean bleeding time being 7.4 minutes and the clotting time 16 minutes by Bürker's method. Traum *et al.* (1931) found that in five male bleeders the clotting time ranged from 105 to 12 minutes, average 60 minutes; in three women bleeders the time was 26–12 minutes, average 17.5 minutes.

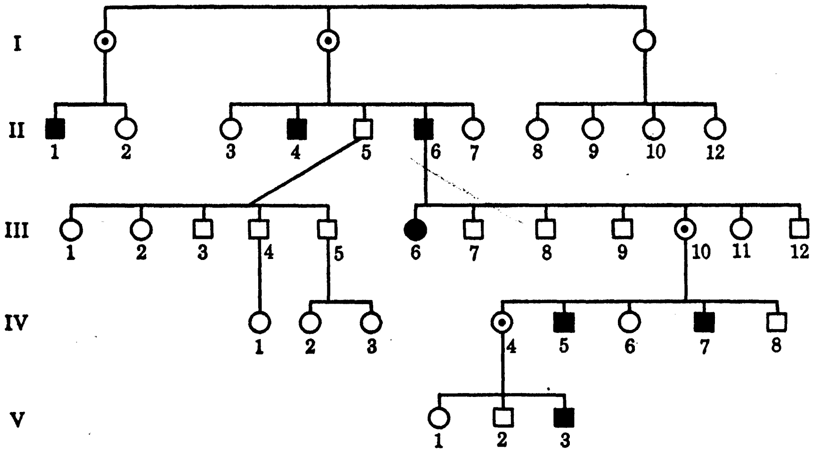


Fig. 217. Pedigree of hemophilia and color-blindness, showing an affected female. (After Madlener)

Another extensive pedigree, of the bleeders of Wald in the Zürich Oberland, going back thirteen generations to a single couple, was compiled by Pfenninger (1934), with twenty-six cases and seven other ancestors who must have been bleeders to account for the inheritance. In this family the law of Nasse is strictly followed, women conductors always being normal. Fonio *et al.* (1937) made a survey of the hemophilic families in the Bern district. Some thirteen pedigrees are recorded with three to five generations. In two families the males transmit (Nasse's law); the rest follow a "weakened Lossen's law," a male occasionally transmitting. Of fourteen female carriers, six show a slight to definite tendency to bleeding, seven are quite normal. Three cases of sporadic hemophilia apparently arose as mutations in families where no bleeders were known, which suggests a high mutation-rate in this area.

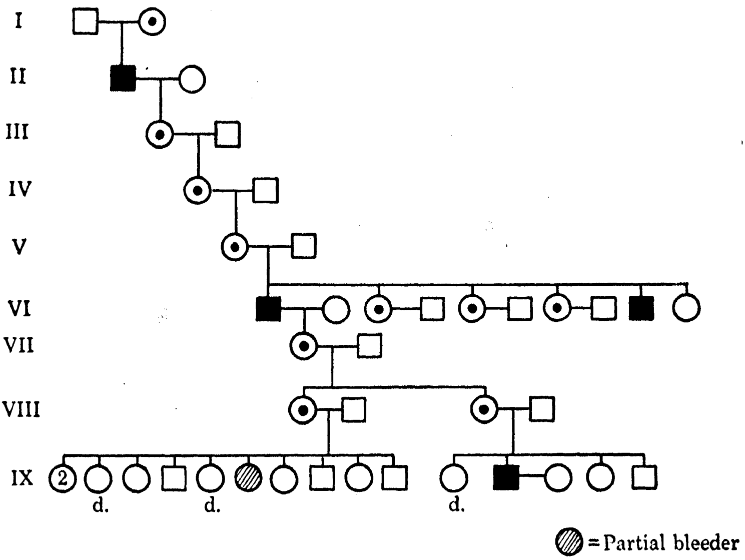


Fig. 218. One line of descent in the bleeders of Tenna. (After Hoessly-Haerle)

A full study of the Tenna family near Zürich by Hoessly-Haerle (1931), with many references to the literature, disclosed some interesting features. First referred to in 1836, this family has been traced back ten generations to 1669. Vieli (1846) gave a short account of the family, recognizing roughly the method of inheritance. There were already twenty cases and they usually died of hemorrhage, hydropsy, gangrene or wounds. Among 866 members, only 48 are bleeders. There is frequently descent from a male bleeder (Fig. 218) and it may run through as many as five successive generations of (normal) conductor females. Occasionally a weak form of female bleeder occurs (Figs. 218 and 219) with, e.g., excessive bleeding from a tooth extraction or from childbirth. This is *differently inherited* (Fig. 219) and may represent a distinct mutation. In either case it is difficult to see why there is a change in the method of inheritance (to irregular dominant) unless the mutation is autosomal and quite independent of the gene for hemophilia. Eight such partial bleeder females occurred in the Tenna pedigrees, some of them (Fig. 219) inherited through a normal father.

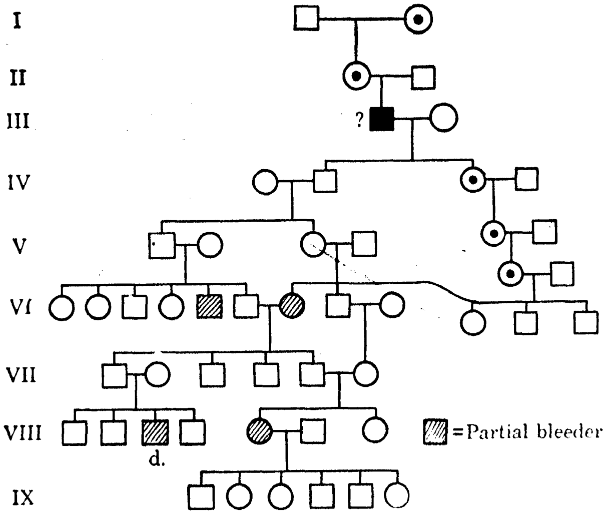


Fig. 219. Another pedigree in the Tenna family, showing partial bleeders. (After Hoessly-Haerle)

Since ordinary heterozygous (conductor) females sometimes show phenomena of bleeding, the condition while sex-linked is neither fully recessive nor fully dominant.

As noted by K. H. Bauer (1922), 19 bleeder families were found to have a low birth-rate (3 children per family), 14 others higher (average 7.9 children per family). Theoretically, marriages between a hemophilic male and a conductor should result in half the daughters being homozygous and supposedly lethal:

$$\begin{array}{ccccccccccc} \underline{X}Y & \times & \underline{X}X & = & \underline{XX} & + & \underline{X}X & + & \underline{X}Y & + & XY \\ \text{♂} & & \text{♀} & & \text{? lethal ♀} & & \text{conductor ♀} & & \text{♂} & & \text{♂} \end{array}$$

There is no evidence, however, that this explanation can be applied to hemophilic families with low birth-rate.

In a colored family (Steiner, 1900), 12 cases (6♂ 6♀) were recorded in four generations. They bled from scratches or from the nose and mouth. One male bled to death and the females were severe bleeders. The condition was strictly dominant and was probably not true hemophilia, although there is no reason why dominant hemophilia should not occur.

Muir (1928) described a hemophilic family in South Africa with eleven generations (1660–1920). Of 610 persons in the pedigree, 46 were male bleeders, and it is stated that the number could be quadrupled if they were all followed up. There was much consanguinity, but this does not affect a sex-linked character.

Birch (1932) has a large pedigree with 15 cases in 7 generations; also a sporadic case of a male hemophilic with four generations of normal ancestors and collaterals. As a mutation, this case is not convincing, as his maternal grandmother bled excessively at childbirth and had several almost fatal hemorrhages at the menopause. Fonio (1934) found in a typical hemophilic pedigree two brothers of a hemophilic who were not bleeders but showed a prolonged coagulation time and fewer platelets than normal. He thinks the clinical severity of the disease is parallel to the number of platelets, and believes that cases of sporadic hemophilia arise from such "latent hemophilics." In another Swiss pedigree with seventeen male hemophilics in three generations (twelve of whom bled to death) the mother and brother of a hemophilic were normal as regards both platelet number and coagulation time. Two large hemophilic families were described in Japan (Kaneko and Amagasa, 1932). Dominant hemorrhagic conditions also occur.

Many other inherited hemorrhagic conditions are now known and some of them can be classified on the basis of different abnormal features shown in bleeding and clotting. Table 18, extended from Farber (1934), will show the basis for some of these discriminations. See also Quick (1941) and Hanhart (1944).

The recognized characteristic features of hemophilia are its usual restriction to the male though transmitted through the female,[2] bleeding into the joints and prolonged coagulation time due to the increased resistance of the blood platelets. The problem of normal coagulation is still far from solved. It has long been regarded as taking place in two steps:

1. Prothrombin + thromboplastin + Ca ions = thrombin.
2. Thrombin + fibrinogen = fibrin.

This fails, however, to explain the nature of these reactions or to take into account possible inhibitory substances in the blood. The thromboplastin is believed to be derived from breakdown of the platelets. Minot and Lee (1916) found in hemophilia a hereditary defect in the platelets, but the organs of a hemophilic had the normal thromboplastin content, the saliva being very active. Howell (1941) showed that normal differs from hemophilic blood plasma in that the latter contains less thromboplastin but normal fibrinogen. Brinkhous (1940),

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[2] This should not, however, be regarded as an essential feature.

TABLE 18

SYMPTOMS OF HEREDITARY HEMORRHAGIC CONDITIONS

	Heredity	*Site of Bleeding*	*Coagulation Time*	*Bleeding Time*	*Tourniquet Test*	*Clot Retraction*	*Platelet Count*	*Platelet Resistance*
Hemophilia	Recessive sex-linked	Joints, skin & mucous membrane	Prolonged	Normal	Negative	Normal	Normal or increased	Increased
Thrombopenic purpura or purp. hemorrhagica*	Irregular dominant	Skin & mucous membrane	Normal	Prolonged	Positive	Delayed	Marked diminution	Normal
Thrombasthenic purpura	Dominant, ♀ affected usually	Skin & mucous membrane	Normal	Prolonged	Positive	Delayed	Normal	Decreased
Minot's & Farber's cases	♂ ♀	Skin & mucous membrane	Normal	Intermittently prolonged	Negative	Occasionally slightly delayed	Normal	Normal
Little & Ayres case	Dominant	Ankle joint etc. with splenomegaly	Normal	Prolonged	——	——	Normal	——
Buckman's purpura	♂ ♀	Skin & nose (infants)	Prolonged	Prolonged	——	——	High	Normal
Purpura simplex	Dominant, recessive, mostly ♀	Ecchymoses	Normal	Normal	Positive	Normal	Normal	——
Levit & Malkova†	Dominant ♂ ♀	Nose & gums	Normal	Prolonged	——	——	Normal	Normal
Fibrinopenia	Recessive?	Infantile	Normal	Normal	——	——	Normal	Normal
Thrombopathy	Dominant, sex-linked	Adults	Normal	Prolonged**	——	Normal	Normal‡	Normal
Giffin's case	♀ sex-limited	Purpura on bruising, epistaxis, cuts	Normal	Prolonged	——	——	Normal or high	Increased
Treves' case	In X & Y	General	Prolonged	Normal	——	——	Normal	——
Hypoprothrombinemia	?	External & internal	Prolonged	——	——	Poor	Normal	——
Fowler's case II.	Irregular dominant	Skin & mucous membrane, intestines & uterus	Normal	Prolonged	——	——	Normal	——
Fowler's case I.	Recessive	Mucous membrane	Normal	Prolonged	——	——	——	——
Telangiectasis	Dominant	Skin & mucous membrane	Normal	Normal	Negative	Normal	Normal	Normal

* Werlhoff's disease
† Defect of capillary epithelium
** Many large platelets.
‡ The clotting and bleeding times as given are the reverse of those in hemophilia, but techniques differ.

in a long review of the subject from the point of view of vitamin K, found that when thromboplastin is added to hemophilic blood in minute quantities, thrombin is formed at the normal rate, so there is no deficiency of prothrombin in hemophilics. Quick, Stanley-Brown and Bancroft (1935) also found prothrombin present in normal amount in hemophilics, while in jaundice the hemorrhagic tendency was due to diminution in this substance. When excess of thromboplastin was present hemophilic blood clotted in normal time. The prolonged clotting time in hemophilia is generally attributed to a failure of the platelets (thrombocytes) to break down with sufficient rapidity. They normally number *ca.* 250,000 per cubic millimeter. When the platelets from hemophilic blood are ground in a mortar and added to hemophilic blood it clots in normal time.

Pennell (1943) has recently found that when normal blood is shed the small platelets aggregate about the larger red cells and become attached to them in large numbers, possibly owing to opposite electric charges. This leads to the rapid disintegration of the platelets, and perhaps also of the red cells, in the process of clotting. He finds that anti-coagulants such as sodium citrate and heparin interfere with this process, and that in hemophilic blood the platelets remain mostly unattached to the red cells, whereas in thrombocytopenic purpura this phenomenon is increased above normal. He suggests that in hemophilic blood the supposed resistance of the platelets to breakdown is because of this failure to become attached to the red cells, which in turn results from some inherited cytological defect of the erythrocytes themselves. Chargaff, Moore and Bendich (1942) have isolated a thromboplastic protein from lung tissue by ultracentrifuging. The manner of its action is uncertain, but it was believed to be enzymatic in nature. The substance also showed marked phosphatase activity.

Lozner, Kark and Taylor (1939) showed that normal human plasma from which the prothrombin and fibrinogen have been removed reduces the clotting time of hemophilic blood, and that the clotting substance is associated with the euglobulins. Recently fibrinogen and thrombin have been isolated from plasma on a large scale (see Edsall, Ferry and Armstrong, 1944). In a further study of the conversion of fibrinogen to fibrin, Robbins (1944) demonstrates two substances, C-fibrin and T-fibrin, which differ in solubility. His conclusions are briefly summarized in the following two lines.

$$\text{Fibrinogen} + \text{thrombase} \longrightarrow \text{T-fibrin.}$$
$$\text{T-fibrin} + \text{ionic Ca} + \text{serum factor} \longrightarrow \text{C-fibrin.}$$

The more soluble T-fibrin is converted to C-fibrin in the presence of a serum factor. For another view of fibrin gel formation see Lyons (1945).

Macfarlane (1945), in a discussion of blood coagulation, points out that the chain theory may be wrong and emphasizes that contraction of the capillaries at a wound is normally a part of the process. The "bleeding time" is prolonged in the purpuras and telangiectasis by deficient vascular contraction, but this contraction is normal in hemophilia, fibrinopenia and lack of prothrombin. Since fibrinogen and prothrombin disappear from the blood stream if their production is inhibited, they must be used up in some metabolic process. Kinase (thromboplastin) and lipoids, which are also necessary for clotting, are present in hemophilic blood. Kinase, which converts prothrombin to thrombin, is an enzyme-like substance present in saliva and highly concentrated in viper venom. Tocantins (1943) finds that the antikinase in hemophilics is 5 to 8 times normal, which would account for the failure of the kinase to act.

The inherited condition of *thrombopenia,* with prolonged bleeding time, arises when the platelets are deficient in number, i.e., less than 100,000 to 200,000 per cubic millimeter. There is still lack of agreement regarding the nature and origin of the platelets (see Bunting, 1932). They have been held to be mitochondria, fragments of red cells or leucocytes, and the extruded nuclei of the red cells. Wright (1910) derived them from cytoplasmic fragments of the megakaryocytes. As they are found (Bürker, 1935) to give the Feulgen reaction, they are presumably composed of chromatin and may well be derived from the nuclei of the megakaryocytes. This would also account for their sticky character, which is especially developed in the chromosomes of Mammals. Mackay (1931), in a careful study of platelet morphology, origin and number, concluded that the platelet is a non-nucleated round or oval disc, diameter 2–3μ, its cytoplasm containing granules. He believed that they arose from megakaryocytes in the bone marrow. Howell and Donahue (1937) think that the giant cells (megakaryocytes) produce the platelets from their cytoplasm, mainly in the lungs. One can only regard the matter as far from settled, with the probabilities strongly favoring their origin from extruded nuclei.[3] It has also been suggested that thromboplastin is a protein-phospholipid complex, in which case they might be derived from mitochondria.

Zeller (1921) claims that differences can be found in the platelets during different diseases and that the platelets of an individual differ *in vivo* in their agglutination capacity. He claims to be able to distinguish seven types of platelets, but his results are not convincing. Stahl (1923) confirms for influenza the general rule that there is a decrease of platelets in acute illnesses. The number may drop to 70–90,000 per cubic millimeter, increasing after the fever to 500,000 or more and then falling to normal. He regarded the platelets as formed from "pseudopodia" torn off from the giant marrow cells.

Purpura is any condition in which local bleeding forms purple patches under the skin and mucous membranes, and *thrombopenic purpura* is characterised by lack of platelets. Werlhof reported the first case in 1735. Brohm in 1881 and Denys in 1887 described the condition, and emphasized that the essential feature is a lowered number of platelets. Hayem noted that the clotting time is normal and Duke showed the prolonged bleeding time. The first splenectomy for this condition was done in 1916, but why it should cure purpura hemorrhagica is unknown. It is probably because the spleen destroys the platelets. Hereditary *purpura simplex* is described by Davis (1939) in eleven families with spontaneous ecchymoses (extravasation of blood, causing discoloration of the skin), mostly in females. In five families they appeared about the time of the climacteric. This is the most benign form of hemorrhagic diathesis. The condition appears to be a somewhat irregular dominant in some families and may be recessive in others. The total number affected in these families is 30 ♀ 2 ♂. In a later paper (Davis, 1941) the condition is recognized as common and 27 families are reviewed with 88 affected members, 84 of them female. The ecchymoses look like bruises. This simple purpura generally appeared at progressively earlier ages in later generations. In two families it was associated with telangiectasis and in two others with epistaxis. In some families the gene might be dominant, with almost complete sex limitation. Of the 88 cases, 79 had purpura simplex, 6 purpura of the rheumatic (Schönlein-Henoch) type, 23 had a history of rheumatic fever, 8 of rheumatoid arthritis, 15 of arthritis, showing the special association between rheumatism and purpura. Thrombopenic purpura is relatively frequent in Japan. Schwartz (1945) recognizes two types, one with, the other without eosinophils in the marrow. The former is relatively benign. He studied thirty cases and regards it as allergic in origin. The latter is without eosinophils and requires splenectomy. The genetic relations of these two types requires examination. They may be the respective heterozygous and homozygous conditions.

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[3] Japa (1943) has recently shown that the nucleus of megakaryocytes obtained by sternal puncture divides successively by mitosis to form 2, 4, 8, 16, 32 nuclei. The cytoplasm breaks down in the later stages to set free these nuclei. This increases the probability that the platelets are derived from this source.

Jürgens (1937) described ten cases (three families) of purpura simplex of a different form from that of Davis. They were also mostly in females, but show skin hemorrhages without alteration in platelet count or in bleeding time. A pedigree in four generations shows 7 ♀ severe (all bled to death) : 9 ♀ mild : 7 ♂ mild : 15 ♂ : 10 ♀. Phillips and Zionts (1942) studied 23 cases of thrombocytopenic purpura, 16 of them (6 ♂ 10 ♀) being idiopathic, the rest symptomatic associated with leukemia, pernicious anaemia or spastic anaemia. The idiopathic cases may be acute or chronic and many of them recover. Funstein (1933) finds changes in various endocrines, especially the ovarian hormones, in cases of thrombopenia.

Hemorrhagic *thrombasthenia* was described in a family by Glanzmann (1918), ten cases in three generations with fewer platelets and less fibrin formation, an ordinary dominant. Minot (1928) described a relatively mild hemorrhagic condition with ecchymoses but normal clotting time and normal platelets, but the bleeding time intermittently prolonged. The family had 10 cases (8 ♂ 2 ♀) in five generations, males mainly affected but inheritance dominant with one skip. Some members suffered from severe epistaxis (nosebleed) in youth. The proponent bled for two weeks from a slight injury to the lip, was afterward operated on for appendicitis without hemorrhage, but bleeding from the wound occurred ten days later. Afterward the bleeding time returned to normal. Minot mentions another family with father, son and daughter in the same condition.

It is evident that Farber's (1934) extensive pedigree represents the same type, simulating hemophilia and purpura. In some kindreds purpura often occurs in the sisters of hemophilics. In this family there are 25 cases (14♂ 11 ♀) in five generations, the sibships numbering 13♂ 11♀ 23♂ 18♀. It is usually observed about the time of puberty in females, somewhat earlier in males, and tends to lessen with age. It varies in severity, but four cases died from bleeding. There is never hemarthrosis (bleeding into joints) and the clotting time is not prolonged. In females the bleeding is chiefly from the uterus and under the skin, causing temporary disablement but far less serious than in the males. There is no telangiectasis nor splenomegaly, but the blood pressure is often high and cerebral hemorrhage is a frequent cause of death. The family is of Germanic ancestry from Alsace-Lorraine. This condition is not hemophilia, since the clotting time is normal. There are three cases of inheritance through affected males, four through affected females and two through normal females. The sibships, where equality would be expected, number 24 affected : 41 normal. The deficiency in transmission is through the males, since female transmitters have 16 affected (12♂ 4♀) : 21 normal children, whereas the children of affected males number 8 affected (1♂ 7♀) : 20 normal. It will be seen that the excess of affected males in the offspring of women is balanced by the excess of affected females in the offspring of affected men. The deficiency of affected females in the offspring of affected women could be accounted for by the partial recessiveness of the condition in women, as seen in generation II. If the gene were in the X-chromosome, however, the single affected son of an affected male could only be accounted for by a cross-over from X to Y combined with incomplete dominance of the normal gene. With the exception of this one male-to-male transmission, the pedigree could be one of sex-linked inheritance with the females generally affected, i.e., dominance of normality incomplete. Like some pedigrees of optic atrophy, it seems impossible to determine whether this interesting pedigree represents a dominant autosomal or a sex-linked condition.

In the family of Little and Ayres (1928) a bleeding tendency inherited as a dominant was accompanied by splenomegaly, the condition thus showing some relation to hemolytic jaundice. The meaning of their dotted symbols is not explained. They may be mild cases. Disregarding these 10, there are 20 cases (9♂ 11♀) in five generations, the inheritance dominant with a single skip. They are severe bleeders, in two cases even into the ankle joint in females, with normal clotting and prolonged bleeding time, the platelets normal in number. One woman died from bleeding following splenectomy. Buckman (1928) described five cases of purpura in infants, two of them brother and sister. The bleeding and clotting times were both prolonged, although the platelets were shown to be capable of clotting hemophilic blood in normal time. Nosebleed was frequent, with ecchymoses all over the body in one case.

The unfortunate term *pseudohemophilia* has frequently been applied to more or less aberrant forms of hemophilia which are inherited as dominant conditions. As many other abnormalities show two or three forms of inheritance, there is no reason why hemophilia should not do the same. For this reason sex-linked inheritance should not be regarded as an essential part of the symptoms. Fowler (1937) describes two such pedigrees. One has 13 cases (9♂ 4♀) in three generations, the sibships numbering 13 affected : 16 normal, heredity dominant with one skip. The affected females bruised easily, suffered from epistaxis and ecchymoses, and the menstruation was profuse. The coagulation time was normal, bleeding time 7½–11½ minutes. Cases were not infrequently fatal and even hemarthrosis occurred. In the second pedigree there were 5 cases (4♂ 1♀) in two sibships, both from normal parents, the bleeding mostly from the mucous membrane. The coagulation time was normal and the bleeding time prolonged. The condition was more severe than in pedigree I and the inheritance would normally be interpreted as recessive.

There is a rare form of bleeding (Levit and Malkova, 1930) in which the defect is not in the blood but in the capillary endothelium. The condition is strictly dominant and one of the names they suggest for it is *heterohemophilia*. It originated as a dominant mutation in IV. 5 and is transmitted through three generations with 11 cases (7♂ 4♀) and two doubtful. The proband, V. 6, was a Russian barrister, born 1886, who suffered from childhood with violent hemorrhages of nose and gums. Later there was severe internal hemorrhage at intervals, producing anaemia, and after splenectomy he became an invalid. There were no petechiae, no thrombopenia, the thrombocytes, coagulation time and fibrinogen were normal. According to these authors, very light forms of bleeding occur in 33.1 per cent of males and 42.1 per cent of females in the Russian population. An essentially similar condition is described by Sack (1936) under the name *status dysvascularis*. This man had very extensive extravasations of blood, due to fragility of the blood vessels, especially the arteries, through lack of connective tissue. A sister, the mother and two of her sisters suffered from *status varicosus*, a related condition dominantly inherited.

Sterren (1934) records a case of a young man of nineteen who had attacks of *meningeal bleeding* at intervals from the age of seven. This was connected with aneurism of the cerebral vessels and the presence of tortuous blood vessels in the fundus of the eye. Other abnormalities also point to general weakness of the mesenchyme, and similar cases in the literature point to its inheritance.

Fibrinogenopenia or even complete absence of fibrinogen is a rare condition producing hemorrhage. Macfarlane (1938) describes a remarkable family with four cases in two generations. Case III. 5 had on one occasion low fibrinogen (75 mg. per 100 cc.) but was not a bleeder, and his aunt had normal fibrinogen (255 mg. per 100 cc.). Case III. 5 married his cousin (the aunt's daughter), who was normal, and three of their four children were affected. One son bled for three days after circumcision but showed no later hemorrhagic tendency and his fibrinogen was high. The daughter bled to death from the umbilicus, while her younger brother had no fibrinogen. We may perhaps regard the father as having inherited low fibrinogen, the complete loss of this substance in his son being an inherited recessive condition following the cousin marriage. Macfarlane (1945) finds two other cases from cousin marriages. Risak (1935) also described four cases of constitutional fibrinopenia in adults, with hemorrhages in infancy. Three cases also had thrombocytopenia. The latter condition has been recorded in a boy of nine years and a girl eight months old. Fibrinopenia can also occur as secondary to liver disease, leukemia or carcinomatosis. Risak ascribes the origin of fibrinogen to the reticulo-endothelial system.

Henderson *et al.* (1945) record the case of a boy who suffered from what they call congenital afibrinogenaemia or total absence of fibrinogen. He had severe hemorrhage and his blood would not clot. A brother and sister were normal and another sister died of umbilical hemorrhage at six days of age. The parents were first cousins and the condition is evidently recessive. The authors found six other cases published. They compare four published cases of hypofibrinogenaemia (fibrinopenia). In these the clotting is normal. Since this was written, another paper has been found (Schönholzer, 1939) which, in the study of another family, confirms that afibrinogenaemia is the homozygous, fibrinogenopenia the corresponding heterozygous condition.

Purpura thrombolytica is the name given by Reimann (1941) to a condition in which the fibrinolytic power of the serum is so high that clots are lysed as fast as they are formed, giving a hemorrhagic effect.

On the Åland archipelago in the Baltic Sea is a population of Swedish Nordics who have been isolated for over 1000 years. Willebrand and Jürgens (1933) found here two Finnish families united by a common ancestor who show what they regard as a new type of constitutional *thrombopathy*, inherited as a sex-linked dominant (Fig. 220). On the mainland is a third family, of Swedish origin, the total number of bleeders being thirty-five. The condition has probably originated here as a mutation and the female members are more affected than the males. The severe form of bleeding is found in females (seven cases) who are homozygous for the condition, which was ultimately fatal in every case. In addition, there are 16 (7 ♂ 9 ♀) milder cases. These are heterozygotes, male and female. In these and other types of female bleeders the bleeding from menstruation is by no means parallel to bleeding from wounds. Such phenomena necessitate a modification of the view that the homozygous condition of hemophilia in females is necessarily lethal. In the above pedigree, the most severe female bleeders often have a normal menstruation time, even when wounds with greatly lengthened bleeding time are bleeding simultaneously.[4] In other cases the menses may be prolonged. The bleeding in these families may begin in infancy, at puberty or later, especially at the climacteric. Nosebleed is its most common form.

The marriage between II. 6 and II. 7 is then XY × $\underline{X}X$ and family C should yield $\underline{X}X$: XX : $\underline{X}Y$: XY, i.e., 1 ♀ : 1 ♀ : 1 ♂ : 1 ♂. The actual numbers in this family are 3 : 3 : 2 : 3, which is quite in harmony with the theory of a sex-linked dominant as explained by Federley (1916). Similarly, the marriage of two affected (family E) is $\underline{X}X$ × $\underline{X}Y$ and should give $\underline{XX}$: $\underline{X}X$: $\underline{X}Y$: XY, or 1 severe ♀ : 1 mild ♀ : 1 mild ♂ : 1 normal ♂, and the actual numbers are 5 : 0 : 2 : 3. The two normal females in this family were children and would probably develop the symptoms later. The absence of mild female cases is not remarkable with such small numbers, but could also be explained by fluctuation in dominance or by crossing-over. Willebrand (1931), in a later paper, points out that family D, with 2 : 2 : 2 : 0, roughly agrees with expectation, but families A and B do not, A giving 1 : 1 : 0 : 4 : 2 normal ♀, while B gives 0 : 1 : 1 : 3 : 1 normal ♀. It is strange that II. 4 is normal, since a son and a daughter are both affected, but the result could be explained by crossing-over between the Y and the X, as Sirks supposes. In pedigree II there were 13 cases (8 ♂ 5 ♀) in four generations (1 ♀ severe), and in III 12 cases (2 ♂ 10 ♀) in three generations (2 ♀ severe).

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[4] Lozner, Taylor and Taylor (1942) have shown that the fluidity of menstrual blood results from the absence of prothrombin and fibrinogen. It is essentially blood that has already undergone coagulation.

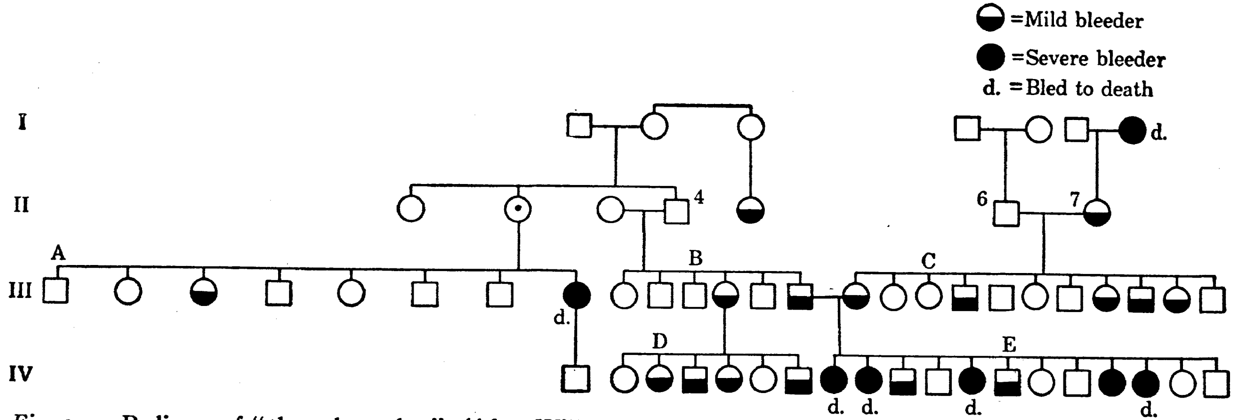

Fig. 220. Pedigree of "thrombopathy." (After Willebrand and Jürgens)

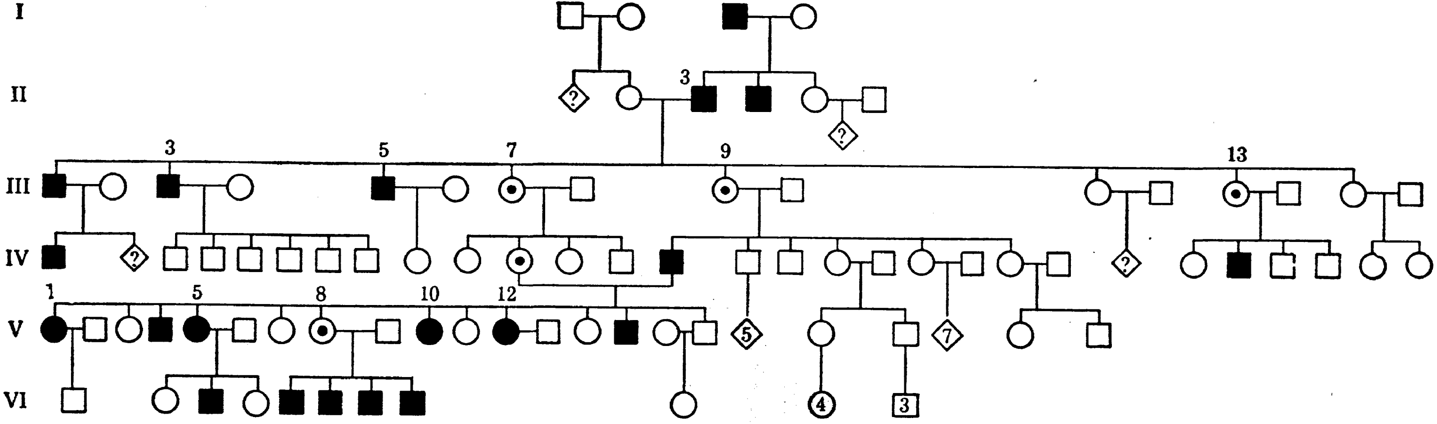

Fig. 221. Treves' pedigree of hemophilia as extended by Handley and Nussbrecher.

A famous pedigree of hemophilia was published by Treves (1886) and has since been extended by Handley and Nussbrecher (1935), who follow Willebrand in calling the condition *pseudohemophilia* on the ground that the method of inheritance differs from the classical sex-linkage in that females are also severely affected. Since the platelet counts were normal, the clotting time prolonged and the bleeding time normal, the condition is clinically hemophilia, and the fact that the method of inheritance is different does not make it a different disease. Not only the symptoms but the manner of inheritance is the same as in Willebrand's pedigree, which has been called *thrombopathy.* The families of Treves, Willebrand, and Little and Ayres agree except that splenomegaly is present in the last.

Treves' pedigree as extended is given in Fig. 221. It is remarkable in that the first three generations show male-to-male transmission, i.e., in the Y-chromosome. Haldane ascribes this to inaccuracy in the record, but this scarcely seems justified. Bulloch and Fildes (1911), on the other hand, dismiss the case as not hemophilia, because it is transmitted from father to son for three generations. Some pedigrees of optic atrophy show a similar apparent change from one form of inheritance to another (see p. 215). Handley and Nussbrecher have made additions to the earlier as well as the later generations of the pedigree. There are, for instance, three hemophilic brothers in generation III, whereas Treves had two. These additions would then seem to confirm the accuracy of the original account. A main feature of Treves' paper was to show that a little girl of six (V. 1) with blue eyes and fair hair had all the symptoms (as far as then analyzed) of severe hemophilia. She bled to exhaustion from a tooth extraction and was in hospital thirteen days. He points out that her parents were first cousins, her father a severe bleeder, and it is now clear that her mother was a carrier. On the assumption that both genes are now in the X-chromosome, we should expect, as in the Åland Islands pedigree, but without dominance of the hemophilic gene, the four types $\underline{XX}$ (hemophilic ♀) : $\underline{X}X$ (carrier ♀) : $\underline{X}Y$ (hemophilic ♂) : XY (normal ♂) in equal numbers; and we have the ratio, 4 : 5 : 2 : 1. Of the five normal females, one is proven to be a carrier, so the whole family fits in very well with expectation and the only difference from the Åland family is in the matter of dominance. If this is correct — and it is the natural interpretation — then it follows that a homozygous bleeder female can not only survive but grow to adulthood and bear a child. Case V. 1 died, however, three hours after the child was born. The clinical details given by Handley and Nussbrecher show that V. 5, 10 and 12 were real hemophilics, bruising easily, bleeding excessively even into joints, and some having epistaxis. The carrier, V. 8, shows similar symptoms to a less degree. The conclusion seems justified that this is ordinary hemophilia with incomplete dominance in the female, whereas in Willebrand's pedigree the dominance was more complete. Bulloch and Fildes (1911), in their monograph, unduly fostered the idea that hemophilic females cannot exist. This has now been proven erroneous by abundant facts.

As regards the method of inheritance, if we assume that the gene was at first in the Y-chromosome, then it must have crossed to the X in III. 3, who had six normal sons. On the other hand, three of the daughters of II.3 were carriers and must therefore have received the gene in their X-chromosome. Of the children of II. 3, the gene would be in the Y-chromosome of III. 1, 5 and in the X of III. 3, 7, 9, 13. The rest of the descent is consistently recessive sex-linked, four homozygous females in generation V being viable. We would seem then to have evidence of crossing-over between X and Y in II. 3, since some of his germ cells must have been $\frac{\mathbf{XH}}{\mathbf{Yh}}$ and some $\frac{\mathbf{Xh}}{\mathbf{YH}}$. It is also necessary to assume variable dominance of **H** over **h** in the male, but that is already known to occur in the female, **h** tending toward dominance, or at least intermediacy, in this pedigree. The fact that **h** can occur in the Y does not mitigate the necessity to account for its ultimate origin through mutation.

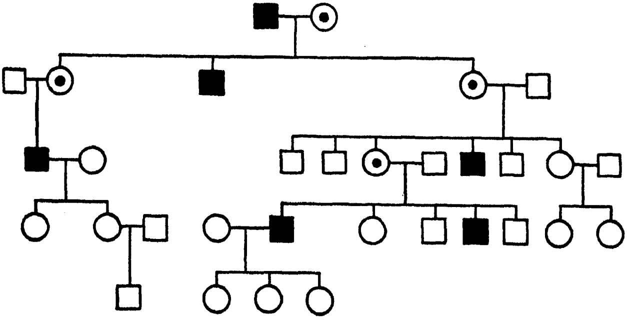

Fig. 222. Marriage between a hemophilic man and a presumed carrier. (After Snyder)

An interesting pedigree (Fig. 222) of Snyder (1932) begins with the marriage of a hemophilic to a normal woman who is assumed to be a carrier. They produced a hemophilic son and two carrier daughters. Such marriages are bound to be very rare, as only 11 per cent of hemophilic males live to the age of twenty-two years. Snyder examined 250 published pedigrees of hemophilia and found only one previous instance of such a marriage (Bullock and Fildes, ped. 407). They produced a hemophilic son and a normal daughter. Snyder's conclusion that there is no evidence of hemophilic females, was reached before the more recent cases were published.

Another peculiar type of hemorrhagic condition, ***recurrent nosebleed***, was found by Giffin (1927). He describes four pedigrees showing 28 cases (16♂ 12♀), its inheritance as a simple dominant, the symptoms including epistaxis (nosebleed), hemoptysis (bleeding from the lungs) and menorrhagia (profuse menstruation). Two other cases were without family history. There were fewer platelets in all cases. In another family (Giffin, 1928) the condition is transmitted from mother to daughter only, with four cases in four generations. Epistaxis, profuse menstruation and profuse bleeding from cuts were symptomatic. One also had gastro-intestinal bleeding with duodenal ulcer and was confined to bed for a month or two at a time. The platelets showed increased resistance, with prolonged bleeding time but normal clotting time.

Wordley (1932) says that nosebleed alone is much more uncommon than when accompanied by telangiectases. He describes such a family, with severe nosebleed beginning in childhood with slight attacks which become more severe. It is a simple dominant pedigree with 9 cases (4♂ 5♀) in three generations. A woman and her mother both finally died (ages fifty, fifty-two) from the severe loss of blood, in spite of transfusions. An early account (Babbington, 1865) described 13 cases (5♂ 8♀) of violent epistaxis in five generations, evidently a simple dominant. One man died from loss of blood. Libman and Ottenberg (1923) describe cases of hereditary hemoptysis, Tidy (1926) cases of hereditary purpuras, and Glanzmann (1925) nine families in which the platelets were not reduced in number but show malformations.

Hess (1916) gives two families with hemorrhagic disorders. In one family two males had hemophilia and a female cousin was a purpuric type of bleeder, having epistaxis almost daily for a year at the age of eight. In the other family a brother showed hemophilia and a sister purpura hemorrhagica. The aetiology and inheritance of these and related conditions needs to be much more carefully studied.

Another pedigree (Fig. 223) under the name *pseudo-hemophilia* has points of interest (Lindsay, 1934). Case III. 2, the proponent, states that all females in her family were bleeders, and seven cases are recorded in four generations. She required the services of a physician for slight wounds and her menstruation was unusually long and copious. Calcium lactate made her blood clot promptly and shortened her menstrual periods to half. *Lack of calcium* seems to have been the defect here. The pedigree is too incomplete to determine the method of inheritance.

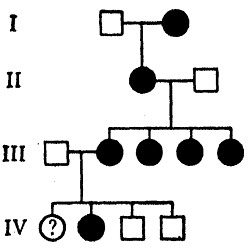

Fig. 223. Pedigree of bleeding confined to females, due to lack of calcium. (After Lindsay)

It might be a case of linked X-chromosomes or of sex-limited descent. Case IV. 1 is too young to show all the symptoms.

Another hemorrhagic diathesis — *deficiency of prothrombin* [5] — is described in a boy whose mother and sister were normal (Rhoads and Fitz-hugh, 1941). There is no such deficiency in hemophilia and the bleeding differs in that the clot retraction is poor. He developed large hematomas from contusions, and the venous coagulation time was 41 minutes. He bled dangerously from slight wounds or tooth extraction and died at eighteen from internal hemorrhages. The prothrombin time was 93 seconds (normal 23 seconds). There was no lack of vitamin K. Another case of hypoprothrombinemia, in a boy and his sister, is described by Murphy and Clark (1944), who cite a further case.

Hess (1916) described two families in which the males have typical hemophilia and the females purpura with a lack of platelets. A form of purpura which differs from Werlhoff's in the absence of thrombopenia is described by Ardashnikov (1938) in a Russian family. There are 10 cases (5♂ 5♀) in four generations, the inheritance being that of a dominant, Three individuals, all males, suffered from throat hemorrhage only, the condition being unlocalized in the other seven.

Bogart and Muhrer (1942) find in pigs a condition with all the clinical features of hemophilia. It is inherited as a simple recessive, but with certain variations ascribed to modifying factors, the platelet number being normal but the thromboplastin deficient. Many pigs die from internal bleeding or bleed to death from a slight wound. Mertz (1942) finds that the capillary resistance of these bleeders is abnormally low, while in heterozygotes it is even higher than normal, indicating that the gene is completely recessive. In a further study of the blood conditions, Muhrer, Bogart and Hogan (1944) measure the platelet fragility by hypotonic solutions and conclude that, as in human hemophilia, the platelets are resistant to breakdown but contain the normal amount of thromboplastin. In another study, Mertz (1943) finds that the prolonged bleeding time is due to failure of injured vessels to constrict. Thus the condition differs from human hemophilia and the single recessive gene produces two defects, one in the platelets, the other in the capillaries.

In a discussion of purpuric conditions in man and animals, Davidson *et al.* (1937) point out the need for a classification of the purpuras on the basis of platelet number. They state that purpura hemorrhagica is known in cats, dogs and cattle and that in horses there is a condition miscalled *equine purpura hemorrhagica* which is accompanied by oedematous swellings. Witts (1937) has also discussed the various hemorrhagic conditions and their classification. He points out that in hemophilic conditions the clotting time is prolonged, whereas in the purpuras it is the bleeding time. In purpura hemorrhagica both platelets and the vessel walls are concerned. As regards treatment, snake venom alone appears successful, although oestrin had some success. Other treatments tried have included liver, ascorbic acid, pectin (from apple skins) and vitamin K for newborn infants in certain cases.

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[5] Vitamin K maintains the normal value of prothrombin in the blood. Bubuk (1943) shows that K_3 from stigmata of maize probably acts by stimulating the synthesis of prothrombin in the liver. K_1 is derived from alfalfa and K_2 from putrefied fish meal. Both are naphthaquinone derivatives and both have been synthesized.

Jersild (1938) finds that Schoenlein-Henoch purpura can be affected therapeutically by vitamin P. This is a crystalline flavone substance, citrin, obtained from rose hips, lemons and oranges. It exerts a specific regulating influence on the permeability of the blood vessels. A woman, age twenty-two, was afflicted for eight years with reduced capillary resistance, the symptoms involving bowels, skin, joints and urinary organs. Ascorbic acid (vitamin C) had no effect, but vitamin P cured her. Jersild suggests that this form of purpura is due to *lack of vitamin P.* Piney (1933) pointed out that the accompanying urticarial rash indicates that the disease is anaphylactoid in nature, not simple bleeding but an inflammatory lesion, such as nephritis or colitis.

Many instances of hemophilia in women have been cited, some of them pretty clearly homozygous, but there are many other cases in the literature, a few of which may be mentioned. Schultz (1930) describes a family (Fig. 224) with six male and one female bleeder in two generations. Case II. 4 often suffered from nosebleed. The blood picture in IV. 4 and IV. 7 showed normal numbers of red cells and thrombocytes and normal amount of hemoglobin. Case IV. 9 had a special form of hemorrhagic diathesis. She died in childbirth. At seven she went to hospital with hemorrhage from a tooth. She often

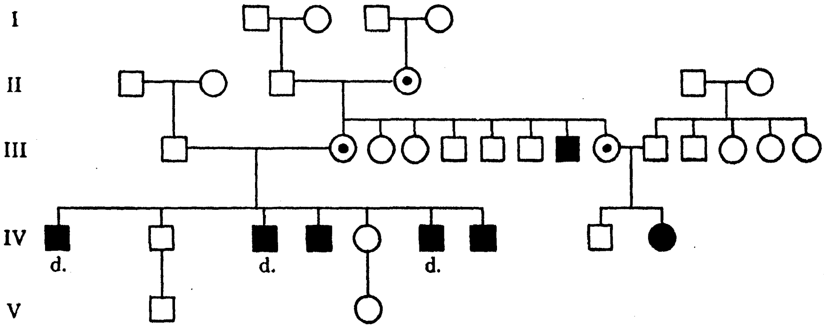

Fig. 224. Hemophilia in six males and a female. (After Schultz)

bled into knee and elbow joints, until they were limited in movement. These symptoms *disappeared at puberty.* The menarche began at seventeen, with periods of normal duration and strength.

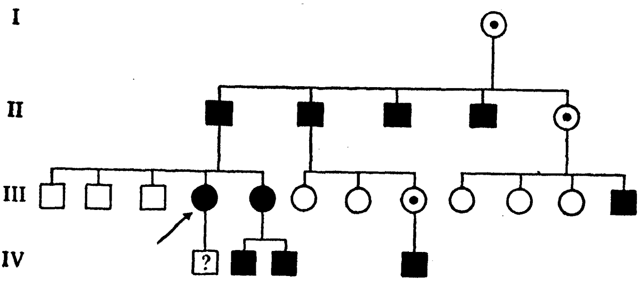

Fig. 225. Pedigree of hemophilia with two hemophilic sisters. (After Foulis and Crawford)

Foulis and Crawford (1934) describe two sisters (III. 4, 5 in Fig. 225) who were trained nurses and belonged to a bleeder family. As in the Warde case, the presence of female bleeders is combined with transmission through the male. Their father was one of four hemophilic brothers. These sisters bled severely from trivial causes. One of them transmitted hemophilia to two sons; blood transfusion evidently saved the life of the other at the birth of her baby son. The clotting time was prolonged and there is no reasonable basis for denying that this was true hemophilia. If the wife of II. 1 happened to be a carrier, then the two daughters might even be homozygous.

Leak (1934) describes a case (Fig. 226) inherited as an ordinary dominant. The blood picture is probably not sufficient to prove hemophilia, although the clotting time is very prolonged. Case I. 1 died of uterine hemorrhage following the birth of twins. Case II. 2 was specially treated before confinement but had severe hemorrhage. All affected members have severe

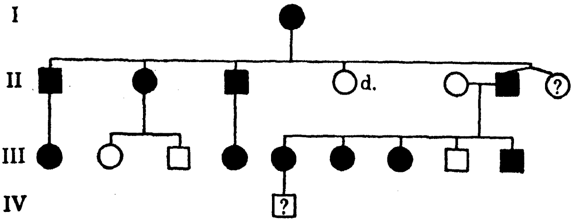

Fig. 226. Female bleeders. (After Leak)

epistaxis which may last for several days. In the third generation bleeding began in infancy. Case III. 5 bled from the mouth at the same time every month until she was two years old. Case II. 5, her parents, grandparents and numerous relatives were all normal, so she was not a carrier. Search for telangiectases disclosed one minute bright red spot anterior to the right tonsil in one individual. The inheritance is obviously dominant, but if the condition were telangiectasis, this would not account for the prolonged clotting time.

One other case with peculiar features may be cited (Joules and Macfarlane, 1938). As the pedigree (Fig. 227) shows, this woman was a sporadic case and could hardly have inherited the condition owing to the large number of normal males among her relatives. Further, she only developed symptoms after the menopause (at fifty-seven). She showed a prolonged coagulation time (43–67 minutes, where the normal time by Lee and White's method is 12 minutes) and bled for a week from tooth extraction. A month later her elbow became stiff and swollen. The tourniquet test produced only a few minute petechieae as evidence of capillary fragility, and the "bleeding time" was never more than 4 minutes. Hence she had all the clinical symptoms of typical hemophilia. Madison and Quick (1945) describe two similar cases in women, which they ascribe to hypoprothrombinemia.

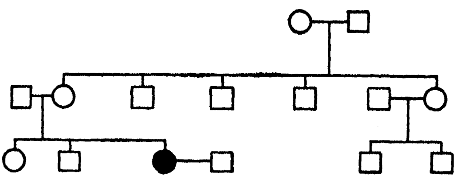

Fig. 227. Pedigree of a female hemophilic, beginning at 56. (After Joules and Macfarlane)

Günder's (1938) family in the Saar region includes twenty-six affected males in six generations, descended from a man who lived at the end of the eighteenth century. The author gives full clinical details and shows that female carriers can be distinguished by tests of the clotting time with Bürker's apparatus. In this extensive pedigree, twelve male bleeders have had children, and at least twenty women have transmitted the condition. This serious defect can only be eradicated if all affected males and carrier females are prevented from having children.

The extensive literature on the physiology of clotting cannot be considered here, but reference may be made to recent papers by Solandt and Best (1940), Dam and Venndt (1940), Günder (1938), Macfarlane (1941), Nygaard (1941), Copley (1941) and Copley and Lalich (1942ab). Bailey, Astbury and Rudall (1943) have recently shown by X-ray photographs that fibrinogen and fibrin belong to the keratin-myosin group of proteins.

Racially considered, hemophilia is characteristic of the Germanic peoples. It has been described in "negro" families (Crandall, 1936), but the accepted cases are always of mixed blood. Heymann (1859) described a Mohammedan family of Indian stock in Palembang, Sumatra, with bleeders in three generations. Three males died, one from a cut lip, another from a finger wound and the third from a tooth extraction. A boy of thirteen nearly bled to death from circumcision, his mother was a bleeder and her brother bled to death following circumcision. Komai (1934) reported from Japan several pedigrees of hereditary epistaxis and several of sex-linked hemophilia. One of the latter is extensive, with twenty cases in four generations; another includes an affected girl.

Attempts have been made to connect hemophilia with particular blood groups, the net result being to show that hemophilics can belong to any blood group. There is, of course, no chance of linkage, since the gene for typical hemophilia is in the X-chromosome while those for the blood groups are in an autosome.

Perhaps the most instructive feature in the medical history of hemophilia is the way in which erroneous ideas, once promulgated, have been adhered to in the face of overwhelming evidence to the contrary. Lossen's "Law" has survived, long after his idea that hemophilic males could not transmit the disease was shown to be false. There is an equal abundance of evidence (contrary to the still surviving view) that females can be bleeders, even in extreme form. It is also clear that the bleeding often bears a definite relation to menstrual phenomena, being in some cases more or less in abeyance during the period of life between puberty and the climacteric.[6] Present evidence shows that a gene for hemophilia, while usually sex-linked, can occasionally be simple dominant or recessive as in many other diseases.

Hereditary *epistaxis* is recorded by Lane (1916), a family in Maine showing the trait with 13 cases (6♂ 7♀) in four generations. It is an irregular dominant with frequent skips. Spontaneous nosebleed occurs almost daily, beginning at adolescence and continuing until eighteen or twenty. Persons showing it are in vigorous health and grow rapidly, often feeling discomfort if the bleeding does not take place. Goldstein (1930) has treated fully the literature of hereditary epistaxis. It can be caused by high altitude, extreme weariness, overexercise or excitement and temporary high blood pressure. The inherited condition is due to weakness of the walls of the capillaries in the nose. Fink (1940) gives a pedigree with ten cases (all males but one) in six generations of a family. The inheritance is dominant, the nosebleed beginning at the age of fifteen. It can be controlled by taking calcium lactate, but of course this does not affect the inheritance.

According to current views, the platelets in the lungs release thromboplastin. Prothrombin, formed in the liver, changes to thrombin in the lungs only in the presence of thromboplastin and calcium ions. The protein thrombin plus the protein fibrinogen produces fibrin which clots the blood.

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[6] On the other hand thrombocytopenic purpura in women may produce severe or fatal menstrual bleeding.

Libman and Ottenberg (1923) described another form of hereditary bleeding, from the lungs — *hemoptysis*. The pedigree includes seven persons with the same histories of repeated profuse bleeding from the lungs, beginning at puberty and continuing at intervals through life. There was no tuberculosis in the whole family. The coagulation time was normal; the condition is not sex-linked and is not fatal. The health is not seriously impaired, and the inheritance is apparently that of a simple dominant.

Multiple Telangiectases (Osler's Disease)

This hemorrhagic condition, also known as *Rendu-Osler-Weber disease*, is a syndrome in which the terminal blood vessels, the capillaries and venules, may become dilated. These vessels have a single layer of endothelial cells covered by a very thin epithelium. They become dilated, forming red spots on the skin, tongue, lips, in the nose or on the cheeks. They may be congenital or may appear on the face in persons exposed to heavy weather, or they may take the form of spider-like naevi and, less frequently, appear on the skin in other parts of the body. They may bleed profusely on the slightest injury. These telangiectases may occur in any part of the body and may cause epistaxis, hematuria, or gastro-intestinal or uterine bleeding.

The disease was first clearly outlined by Osler (1901) who described three cases and recognized its inheritance. Rendu (1896) is generally stated to have described the only previous case. Osler (1908) characterised the disease more fully in a New York family and recognized at least eight families in the literature. He also noted association with cirrhosis of the liver. In all, the inheritance is in accord with a simple dominant, sometimes skipping a generation. In an earlier record, Legg (1876) described a man with epistaxis from boyhood and "naevi." One sister, a son and a daughter were affected. Sometimes an individual member will have epistaxis without the "red spots." Such cases may have telangiectases in the nose. The bleeding is often severe and may cause anaemia. The number of telangiectases varies from many to perhaps a single one. The mortality from bleeding is *ca.* 4 per cent. The blood conditions are normal, the primary defect being a weakness of the blood vessels. Usually the bleeding is not noted until the age of twelve or fourteen and younger children may not show the spots but may develop them later. Cockayne (1933) classifies the condition as a defect in development of elastic tissue. He cites from the literature sibships containing 320 affected : 302 normal, the sex ratio being 178♂ : 190♀. The condition has been described in English, Scottish, Canadian, American, Dutch, German, Scandinavian, French, Italian and Jewish families.

Steiner (1917) gave the history of three families, one of them showing irregular dominance through five generations, and collected twenty-five pedigrees from the literature. In these pedigrees the numbers affected are 90♂ : 75♀, and there is an excess of normals in some sibships. Elastic and muscle fibres appeared to be absent from the dilated capillaries. He believes that the telangiectases appear only after the first hemorrhage.

East (1926) gives two pedigrees of multiple facial telangiectases, with eleven cases in three generations of one family and fifteen in three generations of another. A single dominant gene is concerned, but in one family the parents of the three affected generations were both normal (failure of penetrance or a mutation). Williams (1926) referred to thirty-two known cases and added several of his own. In Mekie's (1927) pedigree the condition is essentially the same and is evidently dominant. The onset of the disease is at about fifteen years of age, the red spots appearing at puberty, especially distributed about the nasal and buccal cavities. Foggie (1928) described this condition accompanied by recurrent hematuria (probably from internal telangiectases) in a family of five generations, again dominant.

In some families the condition is accompanied by enlargement of the spleen, and also the liver in some cases, with increased intolerance to transfusion. Fitz-Hugh (1931) described a Jewish family with 13 cases (5♂ 8♀) in five generations, the inheritance strictly dominant. The enlargement is relatively late and only in the more severe forms of the disease. In this family, four cases died of the disease. Goldstein (1931) has given a full review of the literature, but there is no apparent reason why he should attach his own name to the malady. He found 90–95 families described, with 500–550 persons affected. In a later paper (1936) he describes a family in New Jersey with 18 cases (10♂ 8♀) in five generations. The sibships number exactly 17 affected : 17 normal. One normal father has an affected daughter. *Angiomatosis* does not appear to be a satisfactory name, since the telangiectases contain dilated capillaries but are not tumors resulting from the multiplication of capillaries.

The numerous published accounts indicate that the gene for telangiectasis is not very uncommon. Meikle (1933) cites four cases in three generations of a family, in which there were spots on the lips, swelling of the feet and shortness of breath generally accompanied by epistaxis or other bleeding, and in one case a platelet count below normal. The author mentions six families with thirty affected members in Leeds.

There are pretty clearly both mild and severe forms. Kosiner (1935) describes five cases (all females) in five generations of a family with red spots on face and tongue. Their lives were not shortened, and in the proband nosebleed only began at twenty-eight years of age. In a Swedish family in two generations there were five cases (mother, her brother and three daughters) of multiple *telangiectases of the brain* (Michael and Levin 1936). This is evidently a hereditary disease of the nervous system, producing convulsions and attacks resembling migraine. In one case that died, some of the blood vessels of the brain were becoming calcified and telangiectases of the brain were established. Fifteen similar cases were found in the literature. Schuster (1937) describes another aberrant family in which the arteries and veins as well as the capillaries were abnormal. A woman suffered at intervals from hemorrhages and cutaneous telangiectases in the form of crops of spider naevi every few months, with nosebleed especially before puberty. Her brother had nosebleed and a few spider naevi. Her father also had epistaxis up to the age of forty-five and died of anaemia. Her necropsy showed telangiectases in the skin, nose, mouth, pharynx, larynx, trachea, stomach and duodenum.

Teahan (1939) describes an English family from Yorkshire with 14 cases of telangiectasis (7 ♂ 7 ♀) in six generations. The red spots were so numerous as to be recognized as family marks and the bleeding was very severe, but there was no delay in clotting time. Some cases were accompanied by psoriasis. The condition was dominant, but the remarkable feature is that nearly every member (except three brought in by marriage) appears to have been affected. Alban (1941) has constructed a large family pedigree with 19 cases (5 ♂ 14 ♀) in five generations. The transmission is by both sexes and the inheritance dominant, but in generation III, 9 out of 13 were affected, while in generation IV the sibships numbered only 7 affected to 33 normal, Voyles and Ritchey (1945) record a single case and a family with three cases in three generations. The term "atavism" should not be applied to this condition. It is a simple dominant mutation.

It is clear that the telangiectases of Osler's disease tend to be in particular locations in different families. One will have them mainly on the face or tongue, another will suffer only from epistaxis, another from hematuria or from cerebral telangiectases which usually produce epilepsy and frequently paralysis. Witts (1932) distinguished the hereditary hemorrhagic diathesis from Osler's disease, but the distinction is not sharp.

Penfold and Lipscomb (1943) described a Jewish family in London with nine cases of telangiectasis in three generations, five of them having also elliptocytosis. There was no evidence of linkage between these two dominant conditions.

Campbell (1944) describes a family with 4 cases (1 ♂ 3 ♀) in three generations of telangiectasis accompanied by epistaxis and migraine. Spontaneous bleeding is not common in this disease. It is suggested that epistaxis was brought on by the vaso-dilation of the nasal mucosa which accompanies an attack of migraine.

Snyder and Doan (1944) estimate that over 1000 cases of telangiectasis have now been recorded in about 150 families. Roberts (1941) found a probable case of mutational origin. Snyder and Doan produce good evidence that this dominant condition is lethal when homozygous (**TT**). In a family in which both parents were heterozygous (**Tt**), each having an affected parent, their baby was born with a large port-wine mark on its chest and shortly began to develop telangiectases. When it died at 2½ months its whole body and all internal organs were covered with telangiectases. A very similar case is described in *Lancet* ii:857. 1876. Evidently the condition is only partly dominant in the heterozygote. Wolfsohn (1944) describes a rather extreme case of a man who died at 57, severely anaemic from telangiectases on tongue, lips, cheeks, one eyelid, and pharynx. Gastric examination showed the mucosa covered with red purpuric spots, but none in rectum or lower bowel. His mother had epistaxis and a brother and sister were said to be similar. His wife had twins who died soon after birth, but a daughter was well, so he must have been heterozygous (**Tt**). Cappon (1945) cites a family with 8 cases (4 ♂ 4 ♀) in three generations. Epistaxis caused anaemia and at times there was polycythaemia as an over-compensation.

Some 3% of beef livers in the United States show telangiectases. The origin of this condition is unknown, but Pavcek, Herbst and Elvehjem (1945) show that such livers have a very high vitamin A content as well as much iron and copper. The highest incidence of telang liver is in steers fed on highly concentrated fattening rations.

LITERATURE

Alban, H. 1941. Hereditary hemorrhagic telangiectasia. *Northwest Med.* 40:86–87.

Ardashnikov, S. N. 1938. A hereditary case of a peculiar hemorrhagic diathesis. *J. Hered.* 29:14–16.

Babbington, B. G. 1865. Hereditary epistaxis. *Lancet* ii. 362–363.

Bailey, K., Astbury, W. T. & Rudall, K. M. 1943. Fibrinogen and fibrin as members of the keratin-myosin group. *Nature* 151:716–717.

Bauer, K. H. 1922. Zur Vererbungs- und Konstitutionspathologie der Hämophilie. *Deut. Zeits. f. Chir.* 176:109–184.

Bauer, K. H. & Wehefritz, E. 1924. Gibt es eine Hämophilie beim Weibe? *Arch. f. Gynaekol.* 121:462–501.

Birch, C. L. 1932. Hemophilia. *J. Am. Med. Assn.* 99:1566–1572.

———. 1937. Hemophilia. Clinical and genetic aspects. *Ill. Med. & Dent. Monogr.* No. 4, pp. 151.

Bogart, R. & Muhrer, M. E. 1942. The inheritance of a hemophilia-like condition in swine. *J. Hered.* 33:59–64. Figs. 4.

Boggs, R. 1934. Spontaneous hemophilia. Report of six cases in brothers. *Am. J. Med. Sci.* 188:811–815.

Brainbridge, C. V. 1937. Acquired hemophilia. *Brit. Med. J.* i. 301.

Brinkhous, K. M. 1940. Plasma prothrombin; vitamin K. *Medicine* 19:329–416.

Bubuk, V. V. 1943. The antihaemorrhagic effect of vitamin K_3. *Doklady Acad. Sci. U.S.S.R.* 39:277–279.

Buckman, T. E. 1928. Atypical pathologic hemorrhage in early life. *Am. J. Med. Sci.* 175:307–312.

Bulloch, W. and Fildes, P. 1911. Haemophilia. *Treas. of Human Inher.* 1:169–354. Pls. 17.

Bunting, C. H. 1932. The granular leucocytes, in Cowdry's *Special Cytology*, 2nd Edition, Vol. 2, pp. 699–705.

Bürker, K. 1935. Neuere Ergebnisse über Blutgerinnung. *Centlbl. f. allgem. Pathol.* 63:91–92.

Campbell, A. M. G. 1944. Hereditary familial telangiectasis with epistaxis and migraine. *Lancet* 247:502–503.

Cappon, D. 1945. Hereditary haemorrhagic telangiectasis. *Brit. Med. J.* i. 440.

Chargaff, E., Moore, D. H. & Bendich, A. 1942. Ultracentrifugal isolation from lung tissue of a macromolecular protein component with thromboplastic properties. *J. Biol. Chem.* 145:593–603.

Copley, A. L. 1941. The phenomenon of thixotropy in hemophilic and heparinized blood. *Science* 94:543–544.

Copley, A. L. & Lalich, J. J. 1942a. The experimental production of a hemophilia-like condition in heparinized mice. *Am. J. Physiol.* 135:547–556.

——— ———. 1942b. The influence of blood transfusion and injections of *Bursa pastoris* (shepherd's purse) extract on the clot resistance in two hemophiliacs. *Am. J. Med. Sci.* 204:665–670.

Crandall, N. F. 1936. Hemophilia in the negro. *Am. J. Med. Sci.* 192:745–751.

Dam, H. & Venndt, H. 1940. Observations on the coagulation of blood plasma in haemophilia. *Lancet* 238:70–72.

Davenport, C. B. 1930. Sex linkage in man. *Genetics* 15:401–444.

Davidson, E. C. & McQuarrie, I. 1925. Hemophilia: a study of the blood, the clinical course and the heredity of three cases. *Johns Hopkins Hosp. Bull.* 36:343–356.

Davidson, L. S. P., Davenport, C. & Rabagliati, D. S. 1937. Discussion on purpuric conditions in man and animals. *Proc. Roy. Soc. Med.* 30:715–720.

Davis, Eli. 1939. Hereditary familial purpura simplex. *Lancet* 237:1110–1114.

———. 1941. Hereditary familial purpura simplex. *Lancet* 240:145–146.

DeLacey, M. 1931. Haemophilia in a twin. *Lancet* 221:1074–1075.

Dunn, T. D. 1883. Hemophilia. *Am. J. Med. Sci.* 85:68–83.

East, C. F. T. 1926. Familial telangiectasia. *Lancet* 210:332–334.

Edsall, J. T., Ferry, R. M. & Armstrong, H., Jr. 1944. The proteins concerned in the blood coagulation mechanism. *J. Clin. Invest.* 23:557–565.

Enriques, P. 1922. Hologynic heredity. *Genetics* 7:583–589.

Fairbank, H. A. T. 1930. Hemophilia with haemarthrosis of knee-joint. *Proc. Roy. Soc. Med.* 23:1000–1001.

Farber, J. E. 1934. A familial hemorrhagic condition simulating hemophilia and purpura hemorrhagica. *Am. J. Med. Sci.* 188:815–822.

Federley, H. 1916. Kromosomer och ärftlighet. *Finska Läk. sällsk Handl.* 58:1755–1791. Figs. 33.

Fink, H. K. 1940. Hereditary epistaxis in man. *J. Hered.* 31:319–322.

*Fischer, M. 1932. Zur Geschichte der Bluterkrankheit. *Eugenik* 25.

Fitz-Hugh, T., Jr. 1931. Splenomegaly and hepatic enlargement in hereditary hemorrhagic telangiectasia. *Am. J. Med. Sci.* 181:261–268.

Foggie, W. E. 1928. Hereditary haemorrhagic telangiectasia with recurring haematuria. *Edinb. Med. J.* 35:281–290.

Fonio, A. 1933. Der neue Hämophilie Stammbaum Pool-Pool aus Soglio, Bergell (Kanton Graubunden). *Zeits. f. Klin. Med.* 125:129–143.

———. 1934. Über das Vorkommen einer latenten hämophilen Erbanlage bei klinisch nicht hämophilen Söhnen einer Bluterfamilie nebst weiteren gerinnungsbiologischen Untersuchungen. *Zeits. f. Klin. Med.* 126:424–432.

Fonio, A., Lang, E. & Tillmann, A. 1937. Die Bluterkrankheit im Kanton Bern. *Arch. J. Klaus-Stift.* 12:495–575. Pls. 5.

Fordyce, Sir Wm. 1784. *Fragmenta Chirurgica et Medica.* London. Pp. 41.

Foulis, M. A. & Crawford, J. W. 1934. Female "bleeders." *Brit. Med. J.* ii. 594.

Fowler, W. M. 1937. Hereditary pseudo-hemophilia. *Am. J. Med. Sci.* 193:191–198.

Funstein, L. 1933. Die chronische essentielle Thrombopenie und das endokrine System. *Deut. Arch. Klin. Med.* 175:96–107. Figs. 4.

Giffin, H. Z. 1927. Familial epistaxis without telangiectasia. *Am. J. Med. Sci.* 174:690–695. Figs. 4.

———. 1928. Unusual types of hemorrhagic disease. *Am. J. Med. Sci.* 175:44–49.

Glanzmann, E. 1918. Hereditäre hämorrhagische Thrombasthenie. *Jahrb. f. Kinderhlk.* 88:1–42, 113–141. Pls. 3.

———. 1925. Beiträge zur Kenntnis der Purpura im Kindesalter. *Jahrb. f. Kinderhlk.* 83:271–315, 379–419.

Goldstein, H. I. 1930. Hereditary epistaxis; with and without hereditary (familial) multiple hemorrhagic telangiectasia (Osler's disease). *Internat. Clin.* 40:148–170.

Goldstein, H. I. 1931. Goldstein's heredofamilial angiomatosis with recurring familial hemorrhages (Rendu-Osler-Weber's disease). *Arch. Int. Med.* 48:836–865. Figs. 12 (one col.)

———. 1936. Rendu-Osler-Weber's disease. *Brit. Med. J.* i. 721–722.

Gun, W. T. J. 1938. Hemophilia in the royal caste. *Eugen. Rev.* 29:245–246.

Günder, R. 1938. Gerinnungsprüfungen in einer grossen, bisher nicht beschriebenen Blutersippe. *Arch. f. Rass. Ges.-Biol.* 32:11–69.

Haldane, J. B. S. 1935. The rate of spontaneous mutation of a human gene. *J. Genet.* 31:317–326.

———. 1938a. Congenital disease. *Lancet* 235:1449–1455.

———. 1938b. The location of the gene for hemophilia. *Genetica* 20:423–430.

Haldane, J. B. S. & Philip, U. 1939. The daughters and sisters of haemophilics. *J. Genet.* 38:193–200.

Handley, R. S. & Nussbrecher, A. M. 1935. Hereditary pseudo-haemophilia. *Quart. J. Med.* 28:165–178.

Hanhart, E. 1944. Zur Erbbiologie der hämorrhagische Diathesen. *Arch. J. Klaus-Stift.* 19:543–549.

Hay, John. 1813. Account of a remarkable hemorrhagic disposition existing in many individuals of the same family. *N. England J. Med. & Surg.* 2:221–225.

Henderson, J. L., Donaldson, G. M. M. & Scarborough, H. 1945. Congenital afibrinogenaemia. *Quart. J. Med.* 14:101–111.

Hess, A. F. 1916. The blood and the blood vessels in hemophilia and other hemorrhagic diseases. *Arch. Int. Med.* 17:203–220.

Heymann. 1859. Ein Fall von Haemophilie. *Virchow's Arch. f. Path. Anat.* 16:182–183.

Hoessly-Haerle, G. T. 1931. Der Stammbaum der Bluter von Tenna. *Arch. J. Klaus-Stift.* 5:303–390.

Hogben, L. T. 1931. *Genetic Principles in Medicine and Social Science.* London & New York (Knopf). Pp. 230.

Howell, W. H. 1941. Recent advances in the problem of blood coagulation applicable to medicine. *J. Am. Med. Assn.* 117:1059–1062.

Howell, W. H. & Donahue, D. D. 1937. The production of blood platelets in the lungs. *J. Exp. Med.* 65:177–203. Pl. 1.

Japa, J. 1943. A study of the morphology and development of the megakaryocytes. *Brit. J. Exp. Pathol.* 24:73–80. Figs. 13.

Jersild, T. 1938. Therapeutic effect of vitamin P in Schoenlein-Henoch purpura. *Lancet* 234:1445–1447.

Joules, H. & Macfarlane, R. G. 1938. Pseudo-haemophilia in a woman. *Lancet* 234:715–717.

Jürgens, R. 1937. Die erblichen Thrombopathien. *Ergebn. inn. Med. Kinderhlk.* 53:795–826.

Klug, W. J. 1926. Über die Kirchheimer Bluterfamilien (Mampel). *Deut. Zeits. f. Chir.* 199:145–151.

Kosiner, R. 1935. Über familiäre Telangiektasis. *Klin. Wochens.* 14:713–714.

Lane, W. C. 1916. Hereditary nose-bleed. *J. Hered.* 7:132–134.

Leak, W. N. 1934. Female "bleeders." *Brit. Med. J.* ii. 700, 921.

Legg, Wickham J. 1872. *Treatise on Haemophilia.* London. (Cited from Hoessly-Haerle).

Legg, Wickham. 1876. A case of haemophilia complicated by multiple naevi. *Lancet* ii. 856.

Levit, S. G. & Malkova, N. N. 1930. A new mutation in man, hemophilia-a. *J. Hered.* 21:73–77. Fig. 1.

Libman, E. & Ottenberg, R. 1923. Hereditary haemoptysis. *J. Amer. Med. Assn.* 81:2030–2031.

Lindsay, A. W. 1934. Pseudo-hemophilia. *Eugen. News* 19:145.

Little, C. C. & Gibbons, M. 1921. Evidence for sex-linked lethal factors in man. *Proc. Soc. Exp. Biol. & Med.* 18:111–115.

Little, W. D. & Ayres, W. W. 1928. Hemorrhagic disease; familial bleeding tendency of unusual type with splenomegaly affecting and transmitted by both males and females. *J. Am. Med. Assn.* 91:1251–1252

Lloyd, Bess. 1925. Inheritance of hemophilia. *J. Hered.* 16:28–30. Figs. 2.

Lossen, H. 1876. Die Bluterfamilie Mampel aus Kirchheim bei Heidelberg. *Deut. Zeits. f. Chir.* 7:358–368.

———. 1905. Die Bluterfamilie Mampel in Kirchheim bei Heidelberg. *Deut. Zeits. f. Chir.* 76:1–18.

Lozner, E. L., Taylor, Z. E. & Taylor, F. H. L. 1942. The so-called "coagulation defect" in menstrual blood. *New England J. Med.* 226:418–483.

Lozner, E. L., Kark, R. & Taylor, F. H. L. 1939. The coagulation defect in hemophilia. I. *J. Clin. Investig.* 18:603–608.

Lozner, E. L. & Taylor, F. H. L. 1939. II. *J. Clin. Investig.* 18:821–825.

Lukowski, L. 1927. Five generations of hemophilia. *J. Hered.* 18:212–214.

Lyons, R. N. 1945. Thiol — vitamin K mechanism in the clotting of fibrinogen. *Nature* 155:633–634.

Macfarlane, R. G. 1938. A boy with no fibrinogen. *Lancet* 234:309–312.

———. 1941. The mechanism of haemostasis. *Quart. J. Med.* 10:1–29. Pls. 3.

Macfarlane, R. G. & Scarborough, H. 1945. Discussion on the factors concerned in blood coagulation and their chemical significance. *Proc. Roy. Soc. Med.* 38:399–408.

Mackay, W. 1931. The blood-platelet: its clinical significance. *Quart. J. Med.* 24:285–328.

Madison, F. W. & Quick, A. J. 1945. Hemophilia-like disease in the female. *Am. J. Med. Sci.* 209:443–447.

Madlener, M. 1928. Eine Bluterfamilie. *Arch. f. Rass. u. Ges.-Biol.* 20:390–394. Figs. 2.

Meikle, G. J. 1933. A case of hereditary telangiectasia. *Lancet* 225:863–864.

Mekie, E. C. 1927. Hereditary hemorrhagic telangiectasia. *Brit. Med. J.* i. 423.

Mertz, E. T. 1942. Abnormal capillary resistance in swine suffering from an inherited bleeding disease. *Am. J. Physiol.* 138:136–139.

———. 1943. A blood vessel defect in swine suffering from an inherited bleeding disease. *Am. J. Physiol.* 139:117–122.

Michael, J. C. & Levin, P. M. 1936. Multiple telangiectases of the brain *Arch. Neur. & Psychiat.* 36:514–529. Figs. 9.

Mills, C. A. 1930. The transmission of hemophilia. *J. Am. Med. Assn* 94:1571–1572.

Minot, G. R. 1928. A familial hemorrhagic condition associated witl prolongation of the bleeding time. *Am. J. Med. Sci.* 175:301–306.

Minot, G. R. & Lee, R. I. 1916. The blood platelets in hemophilia. *Arch Int. Med.* 18:474–495.

Mohr, O. L. 1926. Über Letalfaktoren mit Berücksichtigung ihres Verhaltens bei Haustieren und beim Menschen. *Zeits. f. Abst. u. Vererb* 41:59–109. Pl. 1, figs. 10.

Muir, J. 1906. Eight generations of haemophilia in South Africa. *S. Afr Med. Record* 4:300–302.

———. 1928. Heredity in haemophilia in South Africa. *J. Med. Assn S. Africa* 2:599–606.

Muhrer, M. E., Bogart, R. & Hogan, A. G. 1944. Estimation of platele fragility. *Am. J. Physiol.* 141:448–453.

Murphy, I. D. & Clark, J. K. 1944. Idiopathic hypoprothrombinemia *Am. J. Med. Sci.* 207:77–83.

Nasse. 1820. Von einer erblichen Neigung zu tödtlichen Blutungen *Arch. f. Med. Erfahrung im Geb. prakt. Med. u. Staatsarzneikunde* Berlin. Pp. 385–434.

Nissé, B. S. 1927. The evidence of transmission of haemophilia througl the male with a new haemophilic pedigree. *Ann. of Eugen.* 2:25–40

Nygaard, K. K. 1941. *Hemorrhagic Diseases.* Photo-electric study o blood coagulability. London. Pp. 320.

*Osler, W. 1885. Haemophilia. Pepper's *Syst. of Med.* 3:933. London

———. 1901. On a family form of recurring epistaxis, associated witl multiple telangiectases of the skin and mucous membranes. *John Hopkins Hosp. Bull.* 12:333–337.

———. 1908. On multiple hereditary telangiectases with recurrin haemorrhages. *Quart. J. Med.* 1:53–58. Col. pls. 2.

Otto, J. C. 1803. An account of an haemorrhagic disposition existing i certain families. *Med. Repository N. Y.* 6:1–4.

Pavcek, P. L., Herbst, E. J. & Elvehjem, C. A. 1945. The nutritiona value of telang livers. *J. Nutrition* 30:1–9. Fig. 1.

Penfold, J. B. & Lipscomb, J. M. 1943. Elliptocytosis in man associatec with hereditary haemorrhagic telangiectasia. *Quart. J. Med.* 12:157–167. Pl. 1.

Pennell, Samuel. 1943. A platelet-red cell conjugation phenomenon anc its relation to blood coagulation. *Amer. J. Med. Sci.* 205:562–571 Figs. 5.

Pfenninger, H. 1934. Der Stammbaum der Bluter der Wald (Zürche Oberland) 1550–1932, mit besonderer Berücksichtigung der Blutgruppenzugehörigkeit. *Arch. J. Klaus-Stift.* 9:49–72. Figs. 2.

Phillips, J. R. & Zionts, M. A. 1942. Thrombocytopenic purpura. *Amer J. Surgery* 57:51–55.

Pickering, J. W. & Gladstone, R. J. 1924. The coagulability of haemophilic blood. *J. Physiol.* 59:lxv–lxvi. *Lancet* i. 602–604. 1925.

Pickering, J. W. 1928. *The Blood Plasma in Health and Disease.* London, Pp. 247.

Piney, A. 1933. A case of the Schönlein-Henoch syndrome. *Lancet* 225:1144.

Quick, A. J. 1941. The diagnosis of hemophilia. *Am. J. Med. Sci.* 201:469–474.

Quick, A. J., Stanley-Brown, M. & Bancroft, F. W. 1935. A study of the coagulation defect in hemophilia and in jaundice. *Am. J. Med. Sci.* 190:501–511.

Reimann, F. 1941. Purpura thrombolytica. *Acta Med. Scand.* 107:95–104.

Rendu, M. 1896. Epistaxis répétées chez un sujet porteur de petits angiomes cutanés et muqueux. *Bull. et. Mem. Soc. Med. d' Hôp. de Paris* 13:731–733.

Rewcastle, A. G. 1939. Haemophilia in absence of family history. *Brit. Med. J.* ii. 198.

Rhoads, J. E. & Fitz-hugh, T. 1941. Idiopathic hypoprothrombinemia — an apparently unrecorded condition. *Am. J. Med. Sci.* 202:662–670.

Risak, E. 1935. Die Fibrinopenie. *Zeits. Klin. Med.* 128:605–629.

Robbins, K. C. 1944. A study of the conversion of fibrinogen to fibrin. *Am. J. Physiol.* 142:581–588.

Sack, G. 1936. Status dysvascularis, ein Fall von besonderer Zerreisslichkeit der Blutgefässe. *Deut. Arch. Klin. Med.* 178:663–669. Figs. 4.

Schloessmann, H. 1924–1925. Die Hämophilie in Württemberg, genealogische, erbbiologische und klinische Untersuchungen an 24 Bluterfamilien. *Arch. f. Rass. u. Gesells.-Biol.*, 16:29–53, 129–161, 276–303, 353–377.

———. 1930. Die Hämophilie. *Neue Deut. Chir.* Vol. 47. Pp. 306, figs. 60.

Schönholzer, G. 1939. Die hereditäre Fibrinogenopenie. *Deut. Arch. Klin. Med.* 184:496–510.

Schultz, W. 1930. Zur Kenntnis der Hämophilie bei männlichen und auch weiblichen Verwandten. *Fol. Haemat.* 42:310–322.

Schuster, Norah. 1937. Familial hemorrhagic telangiectasia associated with multiple aneurysms of the splenic artery. *J. Pathol. & Bact.* 44:29–39. Pls. 3.

Schwartz, S. O. 1945. The prognostic value of marrow eosinophilia in thrombocytic purpura. *Am. J. Med. Sci.* 209:579–587.

Seddon, H. J. 1929. Haematomyelia associated with haemophilia. *Proc. Roy. Soc. Med.* 23:95–96.

Sirks, M. J. 1937. Haemophilia as a proof for mutation in man. *Genetica* 19:417–422.

Snyder, L. H. 1932. Hemophilia. *Ohio J. Sci.* 32:152–157.

Snyder, L. H. & Doan, C. A. 1944. Is the homozygous form of multiple telangiectasia lethal? *J. Lab. & Clin. Med.* 29:1211–1216. Col. pl. 1.

Solandt, D. Y. & Best, C. H. 1940. Time-relations of heparin action on blood-clotting and platelet agglutination. *Lancet* 238:1042–1044.

Stahl, R. 1923. Über die Blutplättchen bei Infektions- und Blutkrankheiten, insbesondere über die unreifen pathologischen Plättchenformen (Thromboblasten). *Zeits. f. Klin. Med.* 96:182–217.

Steiner, W. R. 1900. Haemophilia in the negro. *Johns Hopkins Hosp. Bull.* 11:44–47.

———. 1917. Hereditary hemorrhagic telangiectasia. *Arch. Int. Med.* 19:194–219. Figs. 30.

Sterren, H. A. van der. 1934. Een merkwaardig geval van spontane, meningeale bloeding. *Nederl. Tijdskr. Geneesk.* 78:3878–3881. Pl. 1.

Studt, H. 1937. Die Bluter von Calmbach. *Arch. Rass. Ges.-Biol.* 31:214–245.

Teahan, W. W. 1939. Hereditary hemorrhagic telangiectasis occurring in six generations. *Ann. Int. Med.* 13:535–543. Figs. 4.

Thomas, C. Price. 1931. Haemophilic joint with glandular enlargement. *Proc. Roy. Soc. Med.* 24:1052.

Tidy, H. L. 1926. On the haemorrhagic diathesis: angio-staxis. *Lancet* ii. 365–369.

Tocantins, L. M. 1943. Demonstration of antithromboplastic activity in normal and hemophilic plasmas. *Am. J. Physiol.* 139:265–279.

Traum, E., Schaaff, G. & Linden, H. 1931. Beitrag zur Frage der Konduktorenbestimmung in hämophilen Familien. *Klin. Wochens.* 10:111–113.

Treves, Frederick. 1886. A case of haemophilia; pedigree through five generations. *Lancet* ii. 533–534.

Vieli, Dr. 1846. Observations sur les Bluters ou hommes saignants. *J. de Med. et Chir. Prat.* 17:340–342.

Voyles, G. Q. & Ritchey, J. O. 1945. Hereditary hemorrhagic telangiectasia. *Ann. Int. Med.* 22:730–736.

Warde, Mildred. 1923. Haemophilia in the female. *Brit. Med. J.* 599–600.

Weinberg, W. 1924. Zur Frage der Letalfaktoren beim Menschen. *Zeits. f. Abst. u. Vererb.* 34:139–140.

Willebrand, E. A. v. 1931. Über hereditäre Pseudohämophilie. *Acta Med. Scand.* 76:521–550.

Willebrand, E. A. v. & Jürgens, R. 1933. Über eine neue Bluterkrankheit, die konstitutionelle Thrombopathie. *Klin. Wochens.* 12:414–417.

——— ———. 1933. Über ein neues vererbares Blutungsübel: die konstitutionelle Thrombopathie. *Deut. Arch. Klin. Med.* 175:453–483.

Williams, C. M. 1926. Hereditary hemorrhagic telangiectasia. *Arch. Derm. & Syph.* 14:1–3.

Witts, L. J. 1932. The hereditary haemorrhagic diatheses. *Guy's Hosp. Repts.* 12:465–474.

———. 1937. The haemorrhagic states. *Brit. Med. J.* ii. 689–692.

———. 1941. The bladder and the laboratory. *Lancet* 240:642–643.

Wolfsohn, H. 1944. Hereditary familial telangiectasis. *Lancet* 247:581.

Wordley, E. 1932. Epistaxis without telangiectasia. *Lancet* 223:1331.

Wright, J. H. 1910. The histogenesis of the blood platelets. *J. Morph.* 21:263–278. Pls. 2.

Zeller, H. 1921. Die Differenzierung der Blutplättchen. *Deut. Med. Wochens.* 47:505–508.

Chapter XV

OTHER INHERITED DISEASES AND ABNORMALITIES OF THE BLOOD SYSTEM

THE RED blood cells or erythrocytes of man, while generally biconcave discs in the blood stream, are remarkable for the changes of shape which they can undergo *in vitro* under experimental conditions. These cells, which have lost their nuclei in all the mammals,[1] are frequently regarded as mere bags of hemoglobin; but their stability of shape and the changes they may undergo, as well as other evidence, leads to the view that they contain a relatively stable framework in which the hemoglobin is held. Normally they are of very uniform shape in the blood stream, but under conditions of anaemia a wide variety of abnormal cell forms may be seen. Ponder (1941, 1942) has recently discussed the causes determining the shape of the red blood corpuscle and the nature of its cell membrane. Casey *et al.* (1934) have found inherited differences in the blood picture of normal rabbits, in the values of basophiles, lymphocytes, red cells and hemoglobin. Closely related breeds, such as the Belgian and English, were found to have similar blood formulae.

In recent years certain aberrant forms of erythrocyte have been found in individuals who showed no symptoms, and these conditions are now known to be inherited. While they are relatively rare, they are generally discovered when the blood is examined for some other purpose. Anaemia is present in some cases, but many individuals with aberrant red cells are perfectly healthy. These unusual cell shapes fall into two series. One, known as *sickle cells* or *sicklemia*, was at first believed to be almost entirely confined to Negroes, but is now known to occur characteristically in the Mediterranean peoples. The other, probably best named *elliptocytosis*, has been found to be present in many races.

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[1] Duran-Jorda (1943) puts forward the unconfirmed claim that the lymphocytes become eosinophil cells; in the cytoplasm of the latter the red blood corpuscles are formed (secreted) in numbers and extruded, the rest of the cell becoming a lymphocyte.

Elliptocytosis

Elliptical human red corpuscles were first observed [2] by Dresbach (1904) in a healthy mulatto student, about 90 per cent of whose red cells were not circular but more or less elliptical. His brother's blood showed only normal cells. It has long been known (Knoll, 1930) that the camels and their relatives, the dromedary, guanaco, vicuña, llama and alpaca are unique among mammals in having elliptical red cells. All the living Camelidae are in this condition. There are also a few large spherical cells, some of them having a nucleus. Among vertebrates below the mammals the red cells are nucleated and strongly elliptical or oval, except in the marine Cyclostomata where they are round. It is also significant that in the human embryo the red cells are nearly all elliptic and a very few of this type may persist after birth. Hence elliptical cells in man may be regarded as a reversion, or rather the persistence of an embryonic condition. As many as 98 per cent of the red cells may be elliptical without clinical effect, but generally the number is not so high. This condition has also been called *ovalocytosis*. The elliptical cells show at once in sealed fresh preparations of blood.

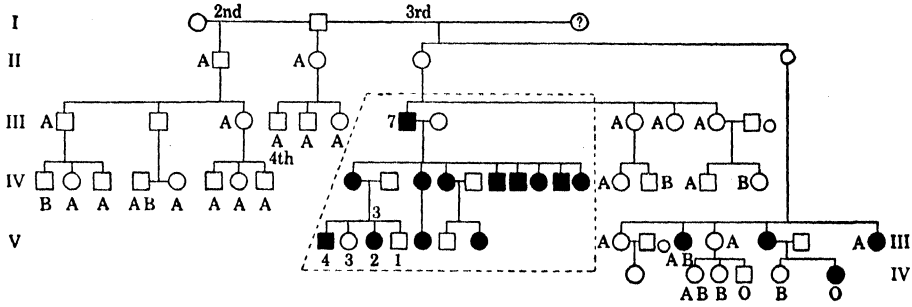

Fig. 228. Pedigree of elliptocytosis in Belgium and (enclosed in dotted line) Montana. (Reconstructed from Hunter and Adams and van den Bergh)

The next observation of elliptical red cells was by Bishop (1914), who recorded them in a brother and sister of a white family and regarded the anomaly as a congenital anatomical defect. Hunter and Adams (1929) described a Dutch family of three generations living in Montana in which there were 13 cases (5 ♂ 8 ♀) of elliptical erythrocytes [3] (part of Fig. 228 enclosed in dotted line). These are all descendants of II. 3. Only one of them (V. 3) showed definite symptoms of anaemia. From this and later evidence the inheritance is clearly dominant, but in generation IV of this family all the eight children were affected. Van den Bergh (1931) traced the Holland branch and the two are combined into one pedigree in Fig. 228. The first marriage of I. 2 was childless. Hunter (1932) afterward added 5 affected members (2 ♂ 3 ♀, a brother of III. 7 and his descendants, not in pedigree) and van den Bergh (1931a) added four more to the Holland branch. Case I. 2 married four times but only the third marriage left descendants with oval red cells, so the third wife (I. 3) must have transmitted the condition; II. 3 emigrated to America with her husband. In the part of the pedigree in Holland the blood groups were also determined. This and other evidence shows that elliptic cells can occur with all four blood groups and there is no evidence of genetic linkage.

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[2] There is some evidence that a case was observed in Königsberg in 1860.

[3] It should be pointed out that the symbols introduced by these writers are extremely confusing and difficult to decipher. It is to be hoped that the international symbols (see p. 4) will be adhered to in future.

Lawrence (1931) described three more cases — a white woman, a colored woman (Fig. 229) and a Russian Jew. His four children and four grandchildren were examined, one child having the same condition as her father, i.e., some "sausage-shaped" cells with rare typical sickle cells, while one grandchild showed a few oval cells. These aberrant forms are frequently grouped together under the name *poikilocytosis*. Other scattered cases were described in the United States and in Berlin. Cheney (1932) described a family in San Francisco with 14 cases (10 ♂ 4 ♀) in three generations. The condition was a strict dominant with no skip of a generation, the sibships numbering 14 affected : 14 normal. The family was Italian, the parents of the first generation known to be affected being born in Palermo and there was no evidence of anaemia in any case. In another study, Terry, Hollingsworth and Eugenio (1932), in an analysis of the fifty-two known cases, found the sexes equally affected and a generation occasionally skipped. The elliptical cells were found to be heavier than the round ones and more

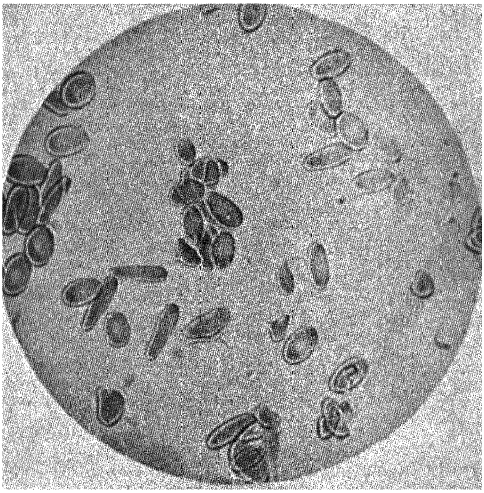

Fig. 229. Sealed preparation of blood showing elliptical red cells. (After Lawrence)

resistant to hypertonic salt solution. In an autopsy case oval cells were found in heart muscle, spleen and suprarenals. They were also present in the marrow of the femur, which was reddish purple and semifluid instead of yellow and thick in consistency. The condition was regarded as an atavistic mutation. In a Swiss family (Leitner, 1943) seven out of eight persons in three generations had elliptocytosis and two of them showed hemolytic anaemia.

Grzegorzewski (1933) described a family in Danzig with 21 cases (11 ♂ 10 ♀) in five generations, strictly dominant with no skip. He recorded sixty cases reported in America and Europe in whites, negroes and colored, in Americans, Dutch, Germans and Swiss of ages three to seventy-six years. Rotter (1933) reported a similar dominant pedigree with 9 cases (5 ♂ 4 ♀) in three generations in a family in Costa Rica with no negro blood. McCarty (1933) reported eleven cases from Alabama. Four of these were discovered in the routine examination of *ca.* 10,000. The other seven are relatives of three of these. In three generations of a family McCarty found 48 per cent elliptic cells in the grandfather, 15 to 17 per cent in the daughter and 10.3 per cent in the grandson. She makes the suggestion that the original mutation shows blending inheritance in later generations. This is hardly in accord with the strict dominant inheritance through several generations nor with the wide variation within a sibship. Hunter and Adams (1929) found 91 per cent and 17 per cent elliptic cells respectively in two sisters. The cause of these wide variations is still unknown. McCarty found that if the red cells are washed with lecithin they all become round, and concluded that the elliptical shape was an end (destructive) stage of all red cells.

Pollock and Dameshek (1934) described a Jewish family from western Russia in which the red cells were round, oval, elongated, sickled or oat-shaped with long pointed ends from which long filaments extended, i.e., sickle-shaped. The condition was found in two sisters, a brother and the mother. Among 135 other patients examined, in three of them 3 per cent of the red cells were oval or elongated; in four others 1 per cent of the cells were so affected; in eleven 0.25 to 0.5 per cent of cells were elongated; in thirty 0.1 to 0.2 per cent; while in 40 persons there was one abnormal red cell per 1000 and in the remaining 47 no abnormal cells were found. The occurrence of 3 per cent or less of abnormal cells is therefore widespread and no special significance need be attached to it. These observations also show that transitions can occur between oval or elliptical and sickle cells.

These authors regard oval, elongated and sickled cells and sickle-cell anaemia as four gradations of abnormality determined by heredity. It is conceivable that they may be allelic conditions or mutations at one locus of a chromosome, but the occurrence of so many intergrades makes this decidedly doubtful. Perhaps abnormal red cell shapes with or without anaemia may prove to be two conditions allelic to the normal. In any blood cell preparation the abnormalities generally increase with time. The effects of temperature, pressure, chemicals and other agencies have also been studied. Scriver and Waugh (1930) found that by altering the oxygen content of the blood in the arm by a bandage the sickling increased with decrease in oxygen tension. Sydenstricker (1923) described the case of a Negro with mild anaemia whose red cells ranged continuously from circular to oval and elliptical, occasionally three times as long as broad, 90 to 95 per cent being of abnormal type.

Reference may be made to a few more recent cases of elliptocytosis. Vischer (1938) described a Swiss family with twelve cases in three generations. They were all descended from a single pair five generations back, and the inheritance was dominant. The persons were healthy, with no anaemia or icterus, and the blood groups were O or A. Lieberherr (1938) similarly found twenty-two cases in a family of sixty-six members and concluded that any association with anaemia was accidental. Steinbrinck and Hahnelt (1938) found a brother and two sisters with ovalocytosis, a daughter of one sister also affected. The blood groups were A and O. Iwao and Yoshida (1940) described the first Japanese case, in mother and son.

The literature has been fully reviewed and three large interrelated families of German extraction added in a paper by Wyandt, Bancroft and Winship (1941). Twenty-five per cent elliptic or oval cells has been taken as the border line between normal and affected, but they generally range from 1 to 15 per cent in ordinary persons. A total of 246 cases in 64 families was found in the literature, besides 31 cases in 7 other families which were doubtful because of the small number of elliptic cells present. These cases include Czechs, Poles, Russians, Jews, Germans, Swedes, Danes, Swiss, American whites and Negroes, Javanese (14 cases in a family) and one report from Japan. Transfusion experiments with elliptocytic blood shows that the elliptic cells have a life of only twelve to thirteen days, which is much shorter than that of normal red cells. The conclusion has been drawn that there is a predisposition to anaemia which is usually fully compensated. Others hold that elliptocytosis has no relation to anaemia, but this appears to be incorrect.

In the three German families above-mentioned, eighty-seven members had elliptic cells. As there is some overlapping in the pedigrees it is difficult to determine the exact numbers involved. There appears to be only one case of skipping a generation. The affected are 53♂ : 34♀. In the sibships the ratio is apparently 87 affected : 80 normal. In one family where both parents had elliptic cells there were two sons with round cells, two sons who had died and one daughter whose condition may be significant. She had both elliptic cells and sphaerocytes with other evidence of hemolytic icterus, such as splenomegaly, increased fragility of the red cells, a high number of reticulocytes and jaundice. Probably she was homozygous for the gene for elliptocytosis. The coexistence of sphaerocytes and elliptical cells has been reported in certain other cases.

The incidence of elliptocytosis has been estimated at 0.04 to 3 per cent and is probably not over 1 in 1000. It appears to be higher in Germany than elsewhere. One individual with elliptical cells is recorded whose father and mother, two sisters and their children had only round cells. This is a possible mutation from normal, but the evidence is by no means conclusive. Especially in the case of a dominant character, it is important to assemble the evidence of origin *de novo* until an unassailable case is found. Those with few elliptic cells in a family with elliptocytosis have been called *part carriers*, but as already mentioned, their significance is obscure.

Burks and Wyandt (1941) find a possibility that the gene for oval cells may be linked with that for the AB blood groups, evidence of possible linkage with taste blindness, mid-digital hair and hair color being largely negative, but more evidence is required.

Penfold and Lipscomb (1943) describe the first case of elliptocytosis in England. A Jewish family in London had both elliptocytosis and telangiectasis (*q.v.*). In four generations there were four members with only telangiectasis and five with both. Each disease was dominant with skips and there was no evidence of linkage between them. Fraser Roberts (1945) points out that statistical analysis of this small pedigree furnishes strong evidence against close linkage of these two conditions. It is important that every family in which two inherited abnormalities occur should be fully published so that the presence of coupling or repulsion can be determined.

Sicklemia

Sickle-shaped red cells is another anomaly which is inherited as a Mendelian dominant (Si). It was discovered (Herrick, 1910) in a young Negro from Grenada, West Indies, who was suffering from anaemia. This condition is now called *sickle-cell anaemia* (or drepanocytanemia), while the sickling without anaemia (see Fig. 230) is called *sicklemia.* It is frequently accompanied by acute abdominal pain. In a sealed wet preparation of blood the sickling gradually increases up to twenty-four hours or more. Sickle cells are not present in the blood stream. If the slide is kept for several days the cells gradually revert to their normal shape and this may also happen if the cover slip is previously removed. Probably there is some defect in the formation of these cells in the bone marrow. Murphy and Shapiro (1944) discuss the nature of this defect. In a very recent paper (1945), these authors make a full study of a case of sicklemia in a Negro and find that it is fundamentally an abnormality of erythropoiesis (red cell formation), which differs from sickle-cell anaemia only in having a higher threshold of sickling of the red cells. The sickle cells are rigid and cannot pass through the capillaries, thus producing thromboses with accompanying severe pain. The crisis so produced is relieved when the sickled cells finally are hemolyzed. A new crop of red cells then appears, which tend to sickle as they grow older, thus producing a fresh crisis which lasts about ten days.

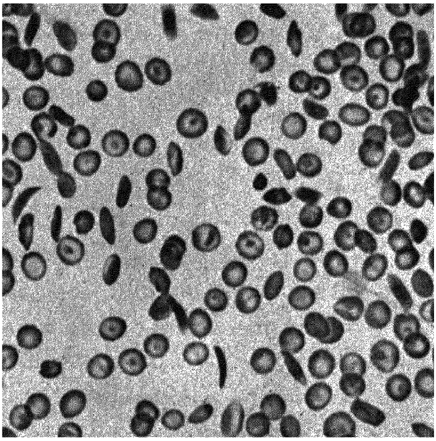

Fig. 230. Photomicrograph of blood from a patient with sickle-cell anaemia. × 240. (Made from a stained preparation from the laboratory of Dr. C. H. Smith)

Sickle cells are most common in the Negro race. From the results of Levy (1929), Diggs *et al.* (1933), Tomlinson (1941) and others, the frequency ranges from 5.6 per cent to 9.6 per cent in American Negroes, the general result being 7.3 per cent in 8453 Negroes. By contrast, 309 whites showed no case of sickle cells. It may be expected, however, that white-skinned segregates from crosses will occasionally have sickle cells in their blood. In Negroes, the cells were found in a premature infant and at ninety-nine years of age. The results were somewhat higher with venous than with capillary blood. The authors confirm that moderate anaemia is almost the rule among colored children and is no more common in those with sickle cells. A Cuban mother and child are reported, both with negroid features and sickle cells. Ryerson and Terplan (1935) reported two Negro families in Buffalo, New York, with sickle cell anaemia. In one the mother and daughter were affected, while the affected in the other family were mother and three of five children, the anaemia being acutely hemolytic. English (1943) found sickle cells in a Bantu from Angola near the border of Northern Rhodesia. Evans (1944) found 15 to 25 per cent of West African Negro soldiers affected. McGavack and German (1944) find sickle cells in 8 per cent of 300 African Negroes at San Juan, Honduras. Tomlinson (1945) finds from 6.5 to 11 per cent in mestizos, browns and blacks in the Canal Zone, Panama, and the British West Indies. The condition is consistently more frequent in females than males and some nine per cent of these cases have sickle-cell anaemia. Sickle cells thus render the individual more liable to anaemia.

The occurrence of sickle cells in the white race is relatively rare but appears to be particularly characteristic of the Mediterranean peoples. Archibald (1926) described an Arab boy in the Sudan with sickle-cell anaemia. His parents both lacked sickle cells, but negroid ancestry is not improbable. Cooley and Lee (1929) reported sickle-cell anaemia in two brothers of Greek descent and Rosenfeld and Pincus (1932) described a family with sickle-cell anaemia (Fig. 230), 5 persons (4 ♀ 1 ♂) in three generations having sickle cells. This family was of pure Italian descent from Calabria. In another family (Haden and Evans, 1937) two sisters, of Sicilian parents, had sickle-cell anaemia. They improved following splenectomy. The symptoms are similar to those of congenital hemolytic icterus, but that is accompanied by *sphaerocytosis*, in which the red cells become spherical.[4] Greenwald and Burrett (1940) have described still another Italian family from Sicily with sickle-cell anaemia. There were 5 cases (4 ♀ 1 ♂) in two generations. The three youngest had sickle cells but no anaemia. The sickling condition is accompanied by decreased fragility of the red cells. Sicilians and South Italians may have Negro blood from the slave days of the Roman Empire.

From these results it appears that sicklemia is found mainly in peoples of Negro origin or belonging to the Mediterranean race. Sights and Simon (1931) described a case of sickle-cell anaemia in an American of Scotch-Irish parentage, but as the relatives were not studied to exclude possible Mediterranean or negroid admixture, this single case can hardly be taken as evidence of sicklemia in the races of northern and central Europe. Greenwald, Spielholz and Litwins (1943) describe sickle-cell anaemia in another Sicilian family from Palermo, with five cases in three generations. Target cells and erythroblastosis were also present. Winsor and Burch (1944) find that sickle-cell anaemia in Negroes leads to a particular habitus mainly characterised by linear build, emaciation and arachnodactyly with a tendency to kyphosis, lordosis and hoop chest.

Poikilocytosis (bizarre forms of red cells) has been observed in cattle (Reid, Huffman and Duncan, 1945). They found 233 cases in 423 dairy cattle (55.1 per cent). When 50 per cent of the red cells were poikilocytes, the health was subnormal. They suggest a nutritional deficiency as the cause, but heredity is probably involved.

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[4] Gillespie (1943) points out that such cells are not truly spherical, but that the more nearly spherical the cell, the less the volume of water it can absorb from hypotonic solutions without stretching of its surface membrane and consequent hemolysis. Castle and Daland showed that differences in hypotonic fragility of the red cells in different mammals can be explained by differences in the dimensions of these cells.

Ponder (1945) shows the remarkable transformations which take place in the red cell in the sickling process. The changes of shape occur in reduced oxygen tension and are reversible.

Thalassemia and Related Jaundiced Conditions

Another hereditary blood disorder which has a clear racial distribution is thalassemia or the erythroblastic anaemia of Cooley. It was also referred to in the early literature as *von Jaksch's disease*, as he first described in 1889 a group of cases of anaemia in infancy or childhood with greatly enlarged spleen, some hepatic swelling, leukocytosis, changes in shape of the red cells and chlorotic anaemia. Cooley (1928), and in a series of earlier papers, showed that children with this type of anaemia develop large numbers of nucleated red cells after splenectomy; they have a sallow complexion, mongoloid features and a thickened skull, are undersized, the serum is frequently pigmented, the anaemia of the hypochromic type (red cells pale), with variation in their size and shape. He found the disease to be confined usually to infants of Syrian, Greek or Italian parentage. Moncrieff and Whitby (1934) described a Greek child in England with thalassemia whose parents were healthy and unrelated. They concluded that the disease is a blood dyscrasia inherited as a Mendelian recessive, occurring in the Mediterranean race and comparable with sicklemia in the Negro.

The three conditions, erythroblastic anaemia of Cooley (thalassemia), congenital hemolytic anaemia (or congenital hemolytic jaundice) and sickle-cell anaemia, are nearly related. Vogt and Diamond (1930) point out that they all show hyperactivity of the bone marrow tissue (marrow hyperplasia) with large numbers of nucleated red cells (erythroblasts) in the blood.

This condition has been identified in the skulls of pre-Columbian Mayan, Peruvian and North American Indians, also in ancient Egyptians and in a French child of the Gallo-Roman period. Whipple and Bradford (1936) found it also in Armenian children. They regard pigment deposits as characteristic of this disease, the red cells being also abnormally thin in some cases. In an earlier paper (1932) they reported three cases and suggested the name *thalassemia* or *Mediterranean disease*. They found typical changes in the bone marrow and suggested that they were analogous to those in pernicious anaemia. A pair of Italian identical twins were both affected, and in an autopsy case the skull was greatly thickened, with histological changes (spongy appearance) also in the ribs and other bones. There was pigmentation (which may be extreme or slight) of liver, pancreas, stomach, kidneys and endocrines. The fundamental change may be in metabolism or perhaps in the red cells. In the later paper they found that the disturbance in pigment metabolism is identical with that in hemochromatosis (*q.v.*) and concluded that the disease is due to some inherited racial defect, with abnormalities in the hemopoietic (blood-forming) tissues, osseous changes as in acromegaly and pigmentary changes as in hemochromatosis. Since the parents appear normal it was believed recessive in inheritance, and sublethal since the death-rate of affected children is very high. Five other cases of Italian children, two of them brother and sister, are described by Koch and Shapiro (1932) in Brooklyn, in addition to eighteen previous cases in the literature. The onset was in early infancy with grave and chronic anaemia accompanied by splenomegaly and icterus (yellow skin). There may be enlargement of cranial and malar bones with an associated mongoloid facies, as well as low hemoglobin content, erythroblastosis, and leukocytosis of varying degree with increase in myeloid and lymphoid cells, but no increase in red cell fragility.[5]

Mills (1938) describes the case of a female Greek child in Montreal whose two brothers had already died of the disease, which supports its recessive character in heredity. He concluded that the primary "cause" of the disease is failure of certain primitive marrow cells to undergo normal maturation. The increased skin pigmentation was found to be due to melanin, not hemosiderin. The essential features of this condition may be characterised as (1) increased skin pigmentation, (2) increase in the marrow cavity of the bones, (3) enlarged spleen, (4) intractable anaemia, (5) hemosiderosis of liver and pancreas. This inherited sublethal syndrome is clearly distinct from both pernicious anaemia and hemochromatosis.

A benign form of thalassemia was found by Wintrobe, Matthews, Pollack and Dobyns (1940) in a Sicilian family in Baltimore. The father and two sons showed splenomegaly, hypochromic microcytic anaemia with icterus, the red cells resistant to hypotonic saline. The mother also showed this increased resistance as well as microcytosis (small red cells). There were very slight changes in the blood of two daughters and slight splenomegaly in two children of one daughter. Similar conditions were observed in two other Italian families in which icterus and splenomegaly were both present. An Italian family in Boston with microcytic anaemia is described by Strauss, Daland and Fox (1941). The erythrocyte count is normal, but the cells vary in size and shape. There are many small cells with hypochromia and increased resistance to lysis by hypotonic saline. X-ray photographs show a granular appearance in the skull and the anaemia is unrelieved by therapy. The inheritance appears to be dominant, with 10 cases (2 ♂ 8 ♀) in two generations, as shown in Fig. 231.

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[5] In 1927, Fanconi described a form of hyperchromic anaemia in three brothers who died in childhood. Dacie and Gilpin (1944) find the same condition in two brothers and their double cousin (hence recessive). The blood of one, who partly recovered, underwent rapid autohemolysis *in vitro*, as in nocturnal hemoglobinuria. Many single sporadic cases are probably recessive outcroppings. The authors point out that abnormalities such as clubfoot and absence of thumbs are frequently associated.

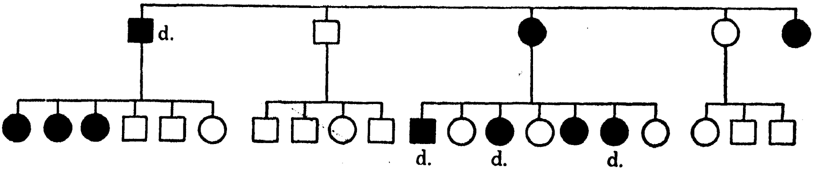

Fig. 231. Pedigree of microcytic anaemia in an Italian family. (After Strauss, Daland and Fox)

In another family from the eastern Mediterranean, Atkinson (1939) described a brother and sister with erythroblastic anaemia, yellow color, weakness and splenomegaly. The hemoglobin was *ca.* 36 per cent and the red cell counts 2,900,000, the cells being hypochromic and microcytic. The condition was distinguished from congenital hemolytic icterus by the increased resistance of the red cells to hypotonic saline. Caminopetros (1938), in the Pasteur Institute of Athens, studied forty-two new cases congenital in Greece and Crete. He concluded that the condition was probably a Mendelian recessive, frequent in Asia Minor. The pedigree of ten cases in four generations indicates rather a dominant with very incomplete penetrance, a generation being skipped five times (Fig. 232). Affected children died within

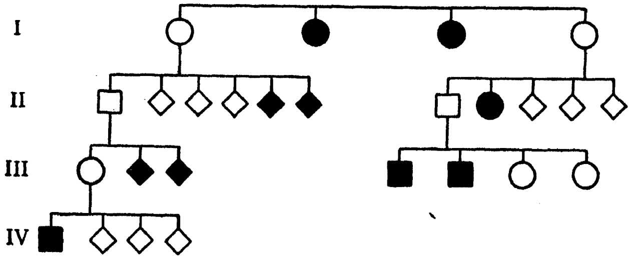

Fig. 232. Pedigree of infantile erythroblastic anaemia. (After Caminopetros)

two years. Many of them had perfect Mongolian features but only two had the Mongolian eye. Caminopetros found increased resistance of the red cells in normal members who transmit and he states that a diseased child always belongs to the same blood group as the carrier parent, thus indicating linkage. Hittmair and Auhuber (1930) give two pedigrees of hemolytic icterus with high fragility of the red cells in which they find slight evidence of linkage with the blood groups. Further investigations are needed to determine possible linkage. The previous literature contained fifty-six cases and the suggestion is noted that the older civilizations were decimated by this inherited disease. Smith (1943) records sixteen families (54 cases) with a dominant mild form which is more common than the severe type. Valentine and Neel (1944) find a total of twenty-seven cases in two Italian and two Sicilian families in America, the inheritance dominant but with a mild and a full-blown condition. The former are heterozygous and the latter homozygous for the gene for thalassemia. From a study of the Italian population (*ca.* 75,000) in Rochester, N. Y., Neel and Valentine (1945) find that the heterozygous condition (thalassemia minor) has a frequency of *ca.* 1 in 25 persons, the homozygotes (thalassemia major) numbering one in 2368 births. Fawdry (1944) describes twenty cases of Cooley's anaemia in children in Cyprus. They had enlarged spleen and liver anaemia, some having mongoloid facies with epicanthus. One child showed dwarfing, infantilism and exophthalmos. Neel and Valentine[6] conclude that thalassemia is recessive, but some heterozygotes show slight anaemia. Recessiveness applies to some pedigrees, but not to all. Diwani (1944) describes two cases of Cooley's syndrome in Egyptian children and one in a Greek child, two having also an enlarged heart. He distinguishes splenic anaemia (von Jaksch disease) as differing in not being fatal and not found in Mediterraneans. Davis (1944) distinguishes between hyperchromic macrocytic anaemia responding to liver therapy (megaloblastic) and macrocytic anaemia associated with normoblastic bone marrow and not responding to liver treatment. He describes three cases in children, in one of which there was a change from hypochromic microcytic to hyperchromic macrocytic anaemia. He found the peripheral blood and the marrow in these cases typical of pernicious anaemia, but believed the cause to be defective assimilation from the alimentary tract. Huber (1939) described three families with 17 cases of what he calls *panmyelophthisis* in three generations, giving details of the numbers of lymphocytes and polymorphonuclears. The condition was regarded as a hereditary constitutional myeloid weakness.

That thalassemia is not confined to the Mediterranean race appears to be shown by the work of Cooper (1941), who stated that in Melbourne, Australia, there are at least three families showing the conditions of this blood dyscrasia, but he makes no mention of their racial affinities. The symptoms include enormously thickened skull bones and mongoloid features. In one family (Fig. 233) 9 cases (3♂ 6♀), including all members but one, were affected in three generations.

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[6] *Records Genet. Soc. Amer.* 1943, No. 12, p. 52.

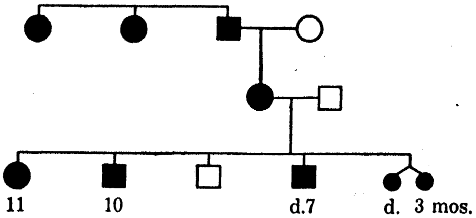

Fig. 233. Pedigree of acholuric jaundice with bone changes. (From Cooper)

Case II. 1 underwent splenectomy at fourteen, but survived and transmitted the condition to five of her six children. In a family with such a large excess of defectives in two generations the condition might be a general constitutional one rather than the result of a heterozygous pair of genes.

Cooley's anaemia is thus instructive genetically, for it shows how the condition can be regarded as recessive if the heterozygotes (having no symptoms) are treated as normal. But examination of their blood shows recognizable abnormal conditions (the minor form), and the gene is, therefore, a partial dominant, sublethal in the homozygous (major) condition.

Acholuric Jaundice and Anaemia

In 1934, three yellow (jaundiced) rats appeared in a litter of thirteen in the colony of rats of Wistar origin at the Connaught Laboratories, Toronto (Gunn, 1938, 1944). From them was derived a strain with hereditary acholuric jaundice — the only known case of hereditary jaundice in animals. The young are normal at birth but become jaundiced in twelve hours or so. Hybrid normals crossed with jaundiced gave a total of 113 yellow : 120 normal, and yellow rats intercrossed bred true. The condition is therefore represented by a single recessive gene. The recessiveness is not complete, however, since the heterozygous carriers show increased fragility of the red cells and reticulocytosis. The mechanism of this increased fragility is discussed by Haden (1934). Unlike human jaundice, rat jaundice does not respond to splenectomy. These rats also show a marked lag in growth, which is attributed to the inability of rats to use carotene as a source of vitamin A; but as already pointed out, there is also retarded growth in children with congenital acholuric jaundice. The acholuric rats also showed marked nervous symptoms, with a wobbly gait or partial paralysis of the hind limbs resulting from vitamin A deficiency.

Acholuric or hemolytic jaundice was first accurately described by Minkowsky in 1900. Claude Wilson had already published in 1890 an account of six cases in three generations of a family under the name "hereditary enlargement of the spleen." Minkowsky described eight cases in three generations of a family which showed enlarged spleen, jaundice with bile absent from the urine but present in the stool, excess of urobilin in the urine, and kidney siderosis. The skin was yellow from birth, and the urine red-brown, but apparently the life was not shortened by this dominant inheritance. Chauffard first showed in 1907 that the red cells were less than normally resistant to hypotonic saline and that reticulocytes (red cells with a visible network) were present in large numbers. In the same year the hemolytic nature of the disease was recognized, i.e., that large numbers of the red cells are destroyed. Based on these discoveries, the hereditary form of acholuric jaundice has been called the *Minkowsky-Chauffard type* and the acquired form (sometimes due to obstruction of the bile duct), which is less common, is alluded to as the *Hayem-Widal disease.* In the latter, autoagglutination of the red cells takes place, but rarely in the former.

Meulengracht (1922), in a monograph on this rare disease, collected fifty cases occurring since 1914. Eight families with thirty-three cases were described in which acholuric jaundice behaved as a simple dominant. In one case the condition had apparently arisen *de novo.* Lord Dawson (1931), in a survey of the disease, regarded hemolysis as the dominant lesion, resulting from red cell fragility. In early stages this is met by overaction of the healthy marrow, the spleen often becomes enlarged and anaemia in varying degrees results. Jaundice may or may not appear.

A recent thesis (Lloyd, 1941) enters again into the physiology of the disease, recognizing a tendency to cholelithiasis in affected individuals. Individuals differ greatly in their susceptibility to trinitrotoluene (Evans, 1941). In an ordnance filling factory there were seven cases of jaundice from T.N.T. (two fatal), the jaundice appearing within six months of exposure.

A large family with a mild form of acholuric jaundice has been studied by Cowen (1936) in Melbourne. It shows 23 cases (12 ♂ 11 ♀) in three generations with much incapacity and invalidism but no deaths from this cause. Splenectomy gives lasting freedom from symptoms. The inheritance is clearly dominant. Cheney and Cheney (1934) describe a family in San Francisco with five cases in four generations, again dominant. Schrumpf (1935) described a family in Oslo with five cases in three generations. They showed heightened serum color but no enlargement of liver or spleen or reticulocytosis and without lowered osmotic resistance of the red cells.

Although acholuric jaundice in man and rats can be taken as parallel mutations, it is remarkable that while essentially recessive in rats it is, generally at least, a dominant in man. As we have seen, however, this distinction can no longer be regarded as fundamental, as it appears to be dependent in some cases on the genetic background of the organism. A dominant pedigree from Campbell and Warner (1926) is given in Fig. 234 with 15 cases (7♂ 8♀) in five generations. Cases III. 1 and III. 2 were apparently normal carriers but their red cells showed the characteristic diminution of resistance to hemolysis by sodium chloride. The blood also contained bile and the urine an excessive amount of urobilin. Here again any sharp distinction between dominant and recessive breaks down.

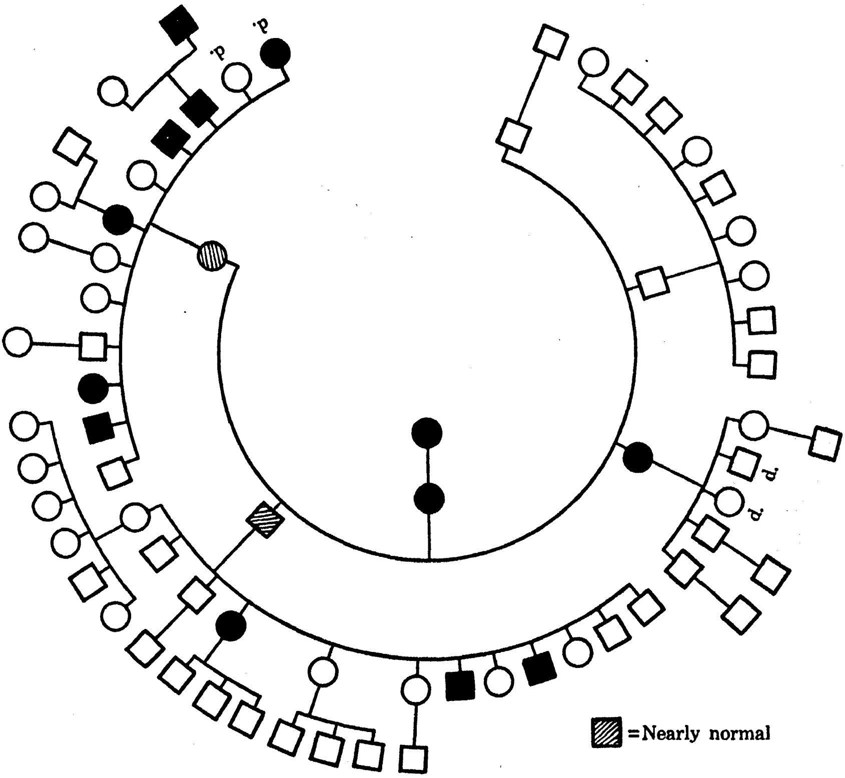

Fig. 234. Pedigree of acholuric jaundice. (After Campbell and Warner)

In a family described by Manson (1928), there were six cases of hereditary icterus in four generations without splenomegaly or shortening of the length of life. The skin and conjunctiva were yellow but there was no bile in the urine. An apparently normal brother had five times the normal amount of bilirubin in his blood, while in affected individuals the bilirubin content was seventeen to thirty times the normal. The family had a characteristically cheerful, placid temperament. Doll (1926) also points out that hemolytic icterus can occur with or without jaundice symptoms, even in the same person at different times.

In this milder form of acholuric or hemolytic jaundice, the health does not suffer and many reach an advanced age. They are jaundiced but not sick, the sexes are equally affected and there appears to be no racial bias. Tileston (1922) showed that the condition was not due to syphilis or tuberculosis but thought the laws of heredity could not be applied to it, since the "congenital" type might only begin in the second decade or later; but of course this is not an argument against inheritance. The acquired type of jaundice may be from obstruction of the bile passages or from infection, intoxication or malignant disease.

Weber (1931) describes a family with seven cases of dominant hemolytic jaundice in four generations. The father, who was affected, died at seventy-six. Only one of his fifteen children showed the disease. This man had ten children, three of whom were affected. One of his daughters transmitted it to two of her five children. Three of these cases had leg ulcers, a not uncommon accompaniment of the disease. Koenan (1938) has another dominant pedigree with 13 cases (5♂ 8♀) in three generations. Every child but one in the three generations was affected and the condition could be produced by pregnancy.

Dameshek and Singer (1941) described two families with familial non-hemolytic jaundice. One was Jewish with three cases in three generations, the other Italian with twelve cases in three generations, including all eight members of one sibship with one affected parent. The inherited condition is believed to be a simple disturbance of liver function. The skin and eyes were more or less yellow, but there was no splenomegaly, sphaerocytosis, reticulocytosis or increased fragility of the red cells, and a low urobilin content in the faeces. Dameshek (1943) described in five families of Italian origin a mild form of Cooley's anaemia, which he calls *target cell anaemia*, from the appearance of some of the red cells.[7] It is dominant in inheritance.

In a critical study of 26 families with 183 members, Race (1942) confirms the dominant inheritance of acholuric jaundice but does not find associated abnormalities unusually frequent. The sibships show a deficiency of jaundiced, which is probably due to their lessened viability, and the homozygous condition may be lethal. He finds some evidence for the existence of *acquired* cases, apart from mutations. Absence of linkage is shown with the A_1A_2BO blood groups, MN, the secreting factor, eye color, attached ear lobes and probably phenylthiocarbamide tasting.

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[7] These target cells are usually thin and Bauer (1945) suggests for this condition the name *leptocytosis*. In all these abnormal cell shapes the life of the red cell is shortened. If new cells are not produced fast enough in the marrow and if the liver fails to dispose of all the liberated hemoglobin, then hemolytic anaemia with icterus will develop. The various red cell shapes constitute genetically a graded series with different degrees of liability to hemolysis, anaemia and icterus. Some authors deny that target cells represent a separate condition.

It appears from the evidence that the mild form of acholuric jaundice is dominant and widespread in Caucasians, while the severe form (thalassemia) is recessive and found mainly in the Mediterranean race, thus following the usual law that the more severe form is recessive. It seems possible that these conditions are allelic, and both may be affected in their expression by the genotype of the family. Thus Beckman and Jäderholm (1932) give an account of a Swedish family in which splenomegaly was present and was followed by operation. There were 15 cases (10 ♂ 5 ♀) in five generations, the condition being dominant with 14 affected to 9 normal sibs.

In another family (Hansen and Klein, 1934) microcytic anaemia is dominant with eighteen cases and seven *formes frustes* in four generations. This family has several other abnormalities, including tower skull, epicanthus, Dupuytren's contracture and accessory mammae. A persistent pupillary membrane occurs in nearly all affected cases. This might be due to linkage of genes. That symptoms of hemolytic jaundice may only develop in old age is shown by the case (Mandelbaum, 1939) of a woman of sallow complexion who, at seventy-five years of age, developed jaundice with microsphaerocytes and increased fragility of the red cells. Splenectomy was followed by recovery.

That newborn babies tend to become jaundiced is well known and the condition is familial. Fordyce and McFee (1924) described a family with three cases of *icterus gravis neonatorum.* Case III. 2 had enlarged liver and in III. 3 both liver and spleen were enlarged. The former died aged two months, the latter at age one day. This is a prenatal form of erythroblastic anaemia.[8] Collis (1934) described a similar family of five children, all of whom were deeply jaundiced shortly after birth and soon died. The symptoms can sometimes be overcome by injections of human serum. In the work of Hawksley and Lightwood (1934) this was believed to be an inherited recessive condition. In a pedigree extending through five generations there were two consanguineous marriages. One resulted in three stillborn births followed by three babies with icterus gravis neonatorum who died in a few days, and finally one normal son. This son married a cousin and one of their two children was jaundiced at six weeks but recovered.

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[8] For an explanation of this in connection with the Rh blood group see p. 700.

Similar sublethal conditions have been described in mice (Grüneberg, 1939), associated with a change in coat color. Dominant spotting is lethal in the homozygous condition (W^1W^1). These mice are anaemic and die a week or two after birth, but if given intraperitoneal injections of blood they grow up into black-eyed whites. An allelic mutation, W^2, is less severe. The heterozygote has white spots on the head and belly. W^2W^2 is viable, a black-eyed white. The red cells of these animals are only about half the normal number, and the hemoglobin is only two thirds the normal amount. W^1W^2 is very similar to W^2W^2 but its anaemia is more severe. W^2W^2 mice have more or less normal birth weights and W^1W^2 are intermediate, W^1W^1 being definitely underweight. In both these anaemic mutations the transition from the megaloblastic erythropoiesis of the foetus to the normoblastic erythropoiesis of the adult is delayed and remains incomplete.

A family with *hepatitis* and *chronic jaundice* was described by Debré (1939). Normal parents had six children, four of them affected. The essential features were hypertrophy of liver and spleen, chronic icterus, with retardation of physical, mental and sexual development. One child was also slightly deaf and another had clubbed fingers. This was regarded as a good example of biliary cirrhosis of the liver, closely analogous to renal dwarfism. Debré gives five short French pedigrees. He found the condition rare in France and Germany, more frequent in England and America but unknown in Spain and Italy, probably most common in Mexico and India, three different types being distinguished. Parsons (1939) described another family with normal parents, in which five of nine children were taken ill during their second decade and died within a few weeks from hepatitis, or inflammation of the liver. The liver showed intense perilobular fibrosis, but there were no brain changes, so the condition was not hepatolenticular degeneration. Bramwell (1916) described a family of 7 children seven to fourteen years old, 4 of whom (1 ♂ 3 ♀) had cirrhosis of the liver, the parents normal. A rise in temperature, with jaundice and ascites (fluid accumulation in the abdominal cavity), led to death in three or four weeks. He regarded it as perhaps related to Wilson's progressive lenticular degeneration.

The condition known as *erythroblastosis foetalis* has been classified into three clinical syndromes and the differences have been considered by Lightwood and Hawksley (1933). There were 15 cases at the St. Louis Maternity Hospital among 22,209 births. Pache (1939) believed in a hereditary form of congenital erythroblastosis and described three cases in a family in two generations, but it is now clear that the explanation is as recounted below. A recent discovery throws light on the nature of this condition. It is now known (see Chap. XVI) that the Rh blood factor is found in *ca.* 85 per cent of white persons and absent in 15 per cent. It is inherited as a Mendelian difference. Levine, Burnham *et al.* (1941) conclude that if the father has the Rh factor and the mother lacks it, the foetus may inherit it from its father. Through the placenta the Rh agglutinogen in the red cells of the child will then produce isoimmunization of the mother's blood. The maternal agglutinins thus formed will pass back through the placenta and agglutinate the red cells of the foetus. Of 153 cases of erythroblastosis foetalis investigated, 93 per cent were found to be due to this cause, which is an indirect result of inheritance. Isoimmunization is also the probable cause of some other habitual abortions and stillbirths.

Eosinophilia

An increase of the eosinophilic leukocytes in the blood can occur under various conditions. It may be caused by allergy, by dermatoses or by the presence in the body of parasites such as Trichina. The normal number of eosinophils in the blood appears to be *ca.* 2 to 5 per cent. Klinkert (1911) in Rotterdam first directed attention to constitutional or familial eosinophilia. He described a family in which the frequencies of eosinophils varied widely. The father was slightly above normal with 6 per cent and the children ranged from 8 per cent to 15 per cent. Bezançon and Moreau (1914) concluded that eosinophilia, when prolonged, is a symptom of poisoning, especially by proteins of animal origin. They could establish no relation between eosinophilia and anaphylaxis. Singer (1933) concludes that eosinophilia is a reaction to substances in the blood, derived from muscle, since it occurred in a case of chronic myositis.

Klinkert (1920) described a father and five children with eosinophil counts ranging from 7 to 15 per cent and hypersensitivity to foods, urticaria, asthma, hay fever, migraine, angioneurotic oedema and gout. Eosinophilia was regarded as an effect derived through the autonomic nervous system. Fanton (1928) described a father and daughter with eosinophilia but no allergy. The mother had 19 per cent eosinophils, and three children 10, 14 and 15 per cent respectively, from no demonstrable cause. Cirio (1926) records the case of a healthy man in Italy with 66 per cent eosinophils, whose brother and five children showed 6 to 15 per cent. Bastai (1923) records a girl of seventeen with 27 per cent eosinophils, the mother, 33 per cent, a sister, 32 per cent; the father and three other sisters were normal. Extraneous causes of eosinophilia were carefully excluded. When marrow eosinophilia is produced by raw liver this is apparently an allergic reaction. In a study of 30 cases of primary thrombocytopenic purpura, Schwartz (1945) found two classes, (*a*) with, (*b*) without, an increase of eosinophils in the marrow. He suggests that the former type is due to some particular allergic agent which can be eliminated. Apley and Grant (1945) find that five cases of tropical eosinophilia with pulmonary disease are probably allergic manifestations from various allergens.

Four striking families were published by Stewart (1933) in which the frequency ranged as high as 33 and 42 per cent. These conditions are known to persist in the individual in some cases for many years. The nature of this constitutional condition and its inheritance is by no means clear. In one family both parental sibships and the two children were high in eosinophils. In the second family the parents showed 2 and 6 per cent respectively, their children 10, 42 and 10 per cent. In another family the parents were 2 and 7 per cent, the children 22, 4, 4, 11, 9, 19 and 13 per cent. There would thus appear to be segregation, but all the affected children except one were much higher than the affected parent (the mother).

A more baffling case was described by Armand-Delille, Hurst and Sorapure (1930). This was an English family which lived in Venezuela until four years before the observations were made. The condition of eosinophilia is very rare in Venezuela apart from worm infections, but one individual tested there gave 40 per cent and another gave 60 and 20 per cent at different times. The family in question, examined in London and Paris, gave the results shown in Fig. 235. Again only one parent is slightly if at all above normal, whereas in four of the children the figures range from 14 to 62 per cent while two are normal. In II. 2, a boy of eight, the tests ranged from 51 to 62 per cent. The children were all perfectly healthy. One can only conclude that the nature of the inheritance here, if it is inheritance, is very doubtful. In the Dutch East Indies high eosinophilia is not uncommon due to infection with *Strongyloides intestinalis*, but the tests for such infection in these children were negative. Tropical eosinophilia can also be produced by filaria infection and by atabrine.

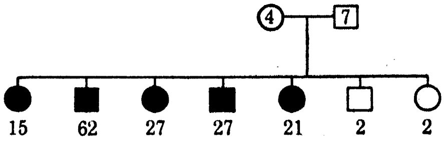

Fig. 235. Percentage of eosinophils in parents and children. (From Armand-Delille *et al.*)

There appear to be only three other families described in the medical literature with similar conditions of high eosinophilia. Palma (1931) has a pedigree with 46 cases (24♂ 20♀) in three generations of a family with 65 members (13 of whom were not examined). This would indicate a dominant inheritance. In India and Egypt it can be acquired, perhaps through infection by a spirochaete or protozoan.

Polycythemia vera (*Vaquez's disease*) was described by Vaquez in 1892 in patients who were cyanosed but without heart disease, having also a high count of erythrocytes and enlarged spleen. The normal number of red corpuscles appears to be about 4.5–6.5 million per cubic millimeter for men and 4–5.6 million for women. Many familial cases of polycythemia have been reported since 1914. It is frequently accompanied by enlarged spleen and the number of corpuscles may be as high as 12,500,000 per cubic millimeter. It is a constitutional condition of the erythropoietic system with a possible basis of endocrine derangement. The face and tongue become very red. The veins of the retina show hemorrhage and distension and the cornea may become bluish.

An Italian immigrant family with benign polycythemia is described by Spodaro and Forkner (1933). Their condition was normal except for the high count of red cells. In this family the father, mother and paternal grandfather all had very red faces. Of the three sons and five daughters, all but three showed excess red cells, the numbers ranging from 6,000,000 to over 8,000,000 per cubic millimeter. Four of the children also had enlarged spleen. There was no leukocytosis and the rest of the blood picture was normal. The inheritance appears to be dominant in this family.

Brockmann (1937) made an elaborate investigation of the condition and its inheritance. He discovered 17 probands and studied hematologically all of their available relatives, i.e., 294 out of over 500. Not a single affected relative was found in any case. Of the seventeen resulting pedigrees, in all but four the condition is probably recessive because they have left a number of descendants (all normal) or, in Fig. 236, because of inbreeding in the ancestry. Two had no living children and two others had only one child (normal). Hence these might conceivably have been dominant mutants, especially as there was no inbreeding in their ancestry. We therefore have a total of two dominant pedigrees, thirteen recessive and four which *might* have been dominant mutations. The absence of other cases among the collateral relatives of such a rare condition is hardly an argument in favor of their recessiveness.

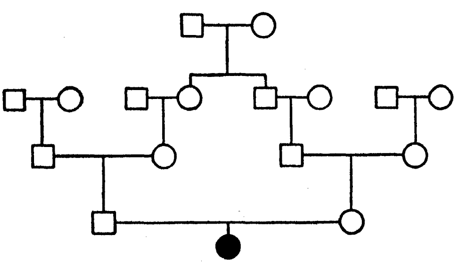

Fig. 236. Ancestry in a case of polycythemia vera. (After Brockmann)

Because there are no cases among the collaterals, Brockmann postulates polymeric recessive genes, but this scarcely seems necessary since there is no evidence of consanguinity except in one pedigree (Fig. 236). The strongest argument for two or more genes being necessary for the production of recessive polycythemia is the fact that five of the single cases occur in rather large sibships of 10, 9, 8, 7 and 7 respectively. On the other hand the other single cases are in sibships of 5, 5, 5, 4, 4, 3, 3, 3, 3, 3 and 1 respectively, in which no more than one mono-factorial recessive need be expected. The isolated individuals with polycythemia did not belong to any particular constitutional type, nor did they have any gastric defect, endocrine derangement or other blood disease.

One must conclude that both dominant and recessive polycythemia occur, the latter being the more usual and perhaps polygenic[9] in some cases. Nadler and Cohn (1939) have since described a family in which polycythemia vera seems clearly to be a single gene recessive. The parents were normal but 4 children (1 ♂ 3 ♀) of the 9 examined showed polycythemia without symptoms. The mother stated that four of her eleven children had red faces from the time of birth. These four showed red cell counts 7.5–8.8 million per cubic millimeter, a high hemoglobin content and hematocrits approximating 150 per cent of normal. The blood picture of the sibs was normal. Engelking (1920) shows clear dominant inheritance in a family with 11 cases (4 ♂ 7 ♀) in three generations. This was chronic polycythemia with effect on heart or kidneys and without high blood pressure.

The condition has been called *morbus coeruleus* because of the cyanosis. Engelking emphasizes the ocular effects. The conjunctiva take a violet color and there are other changes. Fitz, Walker and Branch (1942) describe a case at length and discuss its etiology, which remains obscure. Glazebrook (1944) describes a woman with polycythemia vera and koilonychia. X-ray treatment cured both conditions.

Towle, Coulson, and Fowler (1945) investigated 25 cases. They emphasize the slow development of the disease and regard it as neoplastic, like leukemia. Others believe it is due to an abnormal increase in Castle's intrinsic factor in the presence of a diathesis characterised by deficiency in the central regulation of haemopoiesis.

Polycythemia has been produced in many animals, including dogs, mice, frogs and ducks, by injections of cobalt. Drew and Grant (1945) emphasize the relation of polycythemia to disease of the nervous system. Papilledema (oedema of the optic papilla) is often present. Tinney *et al.* (1945) describe eight cases in which polycythemia vera is associated with gout. This results from the fact that hyperuricemia (excess of uric acid in the blood) frequently arises in polycythemia due to the excess of normoblasts undergoing catabolic changes of their nucleoprotein.

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[9] This term seems preferable to *polymeric* as it is probable that the genes which, on this hypothesis, produce polycythemia are themselves quite diverse in character.

Pelger's Nuclear Anomaly of the Leukocytes

Pelger's anomaly of the leukocytes, which is non-pathologic, was discovered in 1928 in Amsterdam. It consists in an inhibition of nuclear maturing in the myeloid cells of the marrow. Uninucleate leukocytes predominate in the blood stream, and the nuclei are less segmented than normal. The nature of the change in the nuclei is cytologically obscure and an investigation is called for, but the chromatin appears to be in a pycnotic state, with masses present which are not true nucleoli. The anomaly affects all three types of granulocytes — neutrophils, eosinophils and basophils.

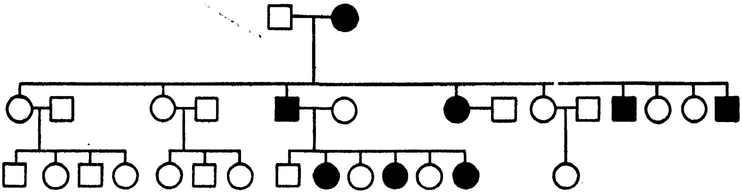

Fig. 237. Pedigree of Pelger's nuclear anomaly of the leukocytes. (Reconstructed from Huët)

Huët (1932) found the condition in a nephew of Pelger's case and described two other families in Amsterdam with this anomaly. The condition is uniformly dominant. One of Huët's pedigrees is given in Fig. 237, 8 cases (3 ♂ 5 ♀) in three generations, sibships 7 affected : 8 normal. In another family four of seven children were affected. The third family had 8 cases (4 ♂ 4 ♀) in three generations, the sibships numbering 7 affected : 9 normal.

By 1935, ten families were known, seven in Holland and one each in Germany, Switzerland and Czechoslovakia, the method of inheritance being the same in all. One case has been recorded in a colored person in the Dutch East Indies. In the Swiss case (Undritz, 1933) 20 to 40 per cent of the leukocytes have a nucleus which is rod-shaped or recalling the condition in young myelocytes. This was the first family described outside of Holland. It consisted of a sister (thirty-two), brother (twenty-eight) and sister (twenty-three) affected. Another sib was not seen.

Leitner and van Leeuwen (1935) described a family with 5 cases (4 ♀ 1 ♂) in three generations. The transmission in this family was through three females, two of whom did not show the anomaly, but one had chronic bronchitis and the other pollen allergy. Zündel (1935) discovered an East Prussian family with 8 cases (5 ♂ 3 ♀) in three generations, the condition being inherited through the father except in one case. Arneth (1937) described two families, one with twenty cases in three generations (sexes not given), the other with three male cases in two generations. He emphasizes that the health of these families needs to be carefully watched. Leitner (1938) in Basle has three pedigrees of Pelger's anomaly, in one Swiss and two Dutch families. They show (1) 4 cases (2♂ 2♀) in two generations, (2) 5 cases (2♂ 3♀) in three generations, (3) 3 cases (2♂ 1♀) in three generations, with simple dominance in every case. Leitner states that two isolated cases have been described which might be mutations or might be a non-inherited (induced) condition.

Tischendorf (1939) reported twenty families in the literature and described two more families in which the anomaly is strictly dominant, one with 8 cases (5♂ 3♀) in three generations, the other with 6 cases (1♂ 5♀) in three generations. Tischendorf finds one male "part carrier" in each family. He believes that the father seldom transmits and then only as a part carrier (i.e., with the anomalous cells less frequent). Females appear to have transmitted about twice as frequently as males, but there is no confirmation that the offspring of males are necessarily part carriers. Schinz (1943), confirming the dominant inheritance, finds that heterozygotes may be either part or full carriers. Nachtsheim has shown that in rabbits the condition is a strict dominant, and homozygotes show a high mortality, their leukocyte nuclei being all round and pycnotic. The survivors have low vitality, anaemia, blindness and deafness as well as shorter limbs. The homozygous condition may be lethal in man too. Sar (1944) cites eight cases (5♂ 3♀) in three generations of a healthy colored family. This makes a total of 89 cases in thirteen families, the sexes equally affected. César (1943) describes a father and four of thirteen children with catarrhal rhinopharyngitis, enlarged lymph nodes, neutropenia and leukocytes with atypical granulations. Four of the children were albinos.

Hegglin (1945) describes a man and his two sons with peculiarities in the blood cells. The megakaryocytes and thrombocytes are changed in form and the platelets take abnormal forms, which leads to a hemorrhagic diathesis and is a form of *thrombopathy* (see Chap. XV). The neutrophils and eosinophils show basophilic irregularities. This is probably a new mutation, dominantly inherited. Of the forty living relatives, thirty-one were examined and found to be normal.

Pernicious anaemia is still in many respects a mysterious disease although first described by Combe in 1822. It occurs in both sexes, generally beyond middle life, chiefly in persons with a large and bulky frame and a strong tendency to fatness. The disease has an insidious beginning; the face gets pale, there is a tendency to breathlessness and the muscles become flabby. This ends in death after several months of extreme debility, although the obesity persists. The volume of the blood is decreased but the coagulation time is increased, so that slight wounds may bleed freely. The serum is golden yellow with bilirubin and the urine is highly pigmented with urobilin and urobilinogen, the skin becoming straw yellow. The reticulocytes which appear in the circulation after hemorrhage have an *increased* resistance to hypotonic saline, the red corpuscles and blood platelets are decreased in number and the fibrin formation is poor, the hemoglobin and leukocytes also being reduced. This description is taken from Piney (1925), who states that the disease is somewhat commoner in men than women and is most frequent between the ages of forty and sixty years. It is extremely rare in children and is said to be unknown in the tropics.

Additional symptoms generally present are achylia gastrica (diminution or absence of gastric juice) and especially achlorhydria (absence of hydrochloric acid from the stomach). Frequently there is also degeneration of the posterior and lateral columns of the spinal cord. Thus the blood system, the stomach and the nervous system are all fundamentally affected. The effect on the spinal cord is evidently secondary, but the mechanism by which it is produced is quite unknown. Possibly it is one of the effects of a single pleiotropic gene. The victims tend to have larger ears, flattened features and light eyes.

Wilkinson and Oliver (1931) describe the case of a man who was invalided from the army in 1857 for persistent diarrhoea. His two daughters, a granddaughter and a great-granddaughter all suffered from this condition, and three of them were shown to have achlorhydria, which was probably present in all five cases. In 76 out of 100 cases of intestinal intoxication (21 ♂ 55 ♀) examined, either achylia or hypo-acidity was found to be present. A pair of male MZ twins developed pernicious anaemia at the age of *ca.* 57, within 18 months of each other (Frank, 1933). Both also were afflicted with paralysis agitans, debility and tower skull.

This disease is clearly related to acholuric jaundice, although there are many differences. As we have seen, the latter has excessive fragility and the former increased resistance of the red cells to hemolysis. In pernicious anaemia there is a reversion to the megaloblastic type of erythropoiesis met with in early embryonic life, while in hemolytic jaundice the red cells are smaller and more nearly spherical than normal. These two types of anaemia are therefore known as *macrocytic* (large celled) and *microcytic* (small celled) respectively. The name *megaloblastic hyperchromic anaemia* has been suggested for the former, since the red cells have at least their normal amount of hemoglobin.

In normal development the liver produces blood cells up to the second month, then the seat of production is gradually transferred until at the end of the sixth month the bone marrow produces all. The liver produces cells of megaloblastic type (like those of pernicious anaemia), about 20 μ in diameter and nucleated. At the end of the fifth month erythrogenesis becomes normoblastic. The normoblasts are much smaller and by extrusion of their nuclei are believed to become the red cells of the postnatal circulation. Pernicious anaemia is thus, as pointed out by Cooke and Hill (1930), a pathological reversion to an embryonic type of blood cells. In this disease erythroblasts (containing a nucleus) are common in the blood stream, and nuclear remnants are frequently seen in the red cells. When granular, these are known as *Howell-Jolly bodies*. They may also take the form of Cabot's rings or a figure of eight. The blood cells not only vary greatly in size (2–15 μ in dried films) but are characteristically oval and deficient in protein. Vacuoles also appear in the cytoplasm of both nucleate and enucleate cells. Auto-agglutination frequently occurs at room temperature, which is ascribed to reduction of differences in potential of the red cells, while rouleaux formation is nearly absent, probably due to the cell shapes, some being biconvex and some almost globular.

In a recent study of blood cells, La Cour (1944) finds that the myelocytes are normally tetraploid. The precursor cells in the marrow may be classed as pre-myelocytes and pro-erythroblasts. They differ in their Feulgen staining and in their ribose-nucleic acid cycles. In pernicious anaemia these differences are accentuated, the chromosomes of the former becoming less spiralized, of the latter tightly spiralized with generally multipolar spindles. The pro-erythrocytes also produce (abnormal) tetraploid megaloblasts. Tetraploid cells undergo no further divisions, and the abnormal relative numbers of red and white cells in pernicious anaemia may be associated with shortage or excess of the nucleic acids.

Japa (1945) finds that the essential abnormality of haemopoiesis in pernicious anaemia is inhibition of cell division, producing (1) decrease in the frequency of mitosis, (2) its earlier cessation. He also finds a lack of proper development of the nucleoli.

It is recognized, of course, that anaemia can also arise from such secondary causes as hemorrhage, infection, carcinoma or toxic conditions. The etiology of pernicious anaemia remains obscure, but there are many records of its familial occurrence (*a*) in several sibs, (*b*) in father or mother and several children, (*c*) in sibs and an uncle or aunt. The great majority of cases are regarded as idiopathic and inherited, due to some slowly developing defect in the hemopoietic organs rather than to a hemolytic process. Several writers have regarded the inheritance as dominant, and the evidence indicates that it is a conditioned dominant, not infrequently skipping a generation. Its familial occurrence was recognized as early as 1876. Cooley (1928) pointed out that congenital hemolytic icterus, sickle cell anaemia (formerly included by some under Jaksch's anaemia) and erythroblastic anaemia form a series, and from the simplest to the most severe there is progressively less benefit from splenectomy.

The racial distribution of pernicious anaemia is very different from that of thalassemia and appears to be as characteristic of the northern European peoples as the latter is of the southern. Friedlander (1934), from a study of five hundred cases in Boston, confirms the opinion that the disease is largely confined to the white race in the temperate zones. The highest percentage of cases is found in Sweden, Denmark and Canada, then England and the United States, but it rarely if ever occurs in Negroes of pure blood, though often present in colored persons. Friedlander finds a constitutional predisposition in persons with fair complexion, light hair and light-colored eyes. Whether this is a matter of genetic linkage or of the fair type being more susceptible, there is no evidence. Its occurrence in negro mixtures would argue against the former alternative. It is supposed to be rare in Chinese, but this is uncertain.

Mustelin (1922) recorded the first case in three generations of a family. Grandmother, mother and daughter were affected, with a number of normal sibs. He concluded that the condition was probably dominant, but not a single-factor condition. Gram (1930) reported on a family in which two died of pernicious anaemia and a third suffered from gastric achylia and severe microcytic anaemia which was improved by large doses of iron. The daughter of this last patient developed pernicious anaemia. The original grandfather, six of his children and ten of his sixteen grandchildren were all examined. One daughter at forty-three showed achylia, Hunter's glossitis, and microcytic anaemia, which became latent pernicious anaemia nine years later, and ten years afterward developed into frank pernicious anaemia which was cured by liver therapy. Another daughter at forty-seven showed gastric achylia and microcytic anaemia, which responded not to liver but to iron. The third daughter at forty-three had an attack of anaemia which was cured by iron, but she had gastric hypersecretion. Of the ten grandchildren, aged nine to twenty-two years, only one had simple anaemia, which responded to iron. All but two, however, showed hypersecretion and hyperacidity in the stomach, so that achylia and pernicious anaemia may appear later.

Gram concludes that pernicious anaemia depends in some way on an inherited condition whose consequences may run through any of these seven phases and end with pernicious anaemia: (1) acid gastritis, (2) slight temporary anaemia, (3) dyspeptic symptoms, (4) glossitis, (5) gastric achylia, (6) severe temporary anaemia, (7) pernicious blood picture (latent pernicious anaemia).

Gastric achlorhydria is described in five members of a French family by Martinez (1927). The two sisters in generation I had chronic diarrhoea and indigestion and ultimately died of gastric cancer. Cases II. 1 and III. 2–5 suffered from chronic diarrhoea with achlorhydria and II. 1 died of gastric cancer. In generation IV, five of the thirteen children had achlorhydria (three without symptoms). Hysterical neurotic temperaments were characteristic of this family. In another family the mother and three daughters had achlorhydria associated with chronic diarrhoea and a hysterical neurotic temperament. The grandfather died of gastric cancer and his two brothers had gastric disturbances. The daughter and granddaughter were hysterical and neurotic.

Among the many reports of families may be mentioned one by Schemm (1940), who studied thirty-two authenticated cases in Montana in six years and cites many previous studies. The familial incidence is shown to be at least 18 per cent and probably much higher because of the difficulties of tracing the inheritance of a disease which generally develops rather late in life. In one family, four brothers and a sister were affected but responded to liver therapy. One sister showed no evidence of the disease and another sib who appeared normal was not seen. Two cases were reported in each of five other families, all sibs except in one instance of mother and son.

Among 645 cases of Stamos (1940) at Ann Arbor, Michigan, fifty-one revealed the disease in one or more other members of the family. In five families three or more children had Addison's pernicious anaemia, while in five other families it was present in three or more members in successive generations although the condition is relatively rare. Meulengracht's (1925) important statistical study with three pedigrees should not be overlooked. Connor (1930) examined the gastric acidity of 109 patients and 154 of their relatives. He found achlorhydria more frequent than in the general population. The incidence was 15.7 per cent among relatives under forty years of age, and 42.3 per cent among those over forty. Maclachlan and Kline (1926) described a family (Fig. 238) with 17 cases (13♂ 4♀) in four generations. A cousin marriage in which five of the thirteen children developed anaemia is recorded by Askey (1940). This family alone suggests a recessive

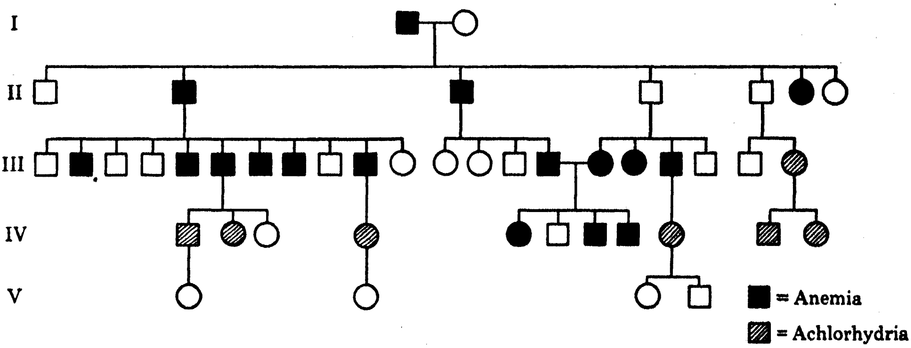

Fig. 238. Family showing pernicious anaemia and achlorhydria. (After Maclachlan and Kline)

inheritance. From an analysis of the literature he lists many other families, in all of which the inheritance appears to be dominant with an occasional skip. In four pairs of MZ twins both members were affected, and in three other pairs anaemia was probably latent in the second member.

Wilkinson and Brockbank (1931) recognized that the condition is usually associated with achlorhydria and that the relatives of pernicious anaemia patients may have only achlorhydria. The latter condition may be found ten to twenty-five years before the onset of anaemia. They found in the literature 127 families with more than one case of pernicious anaemia. In 51 families anaemia and achlorhydria co-existed and in 14 families achlorhydria alone was found. Among the relatives of 291 patients with pernicious anaemia, 70 cases of achlorhydria were found, i.e., 24.1 per cent. Nearly half the cases of achlorhydria have also achylia gastrica. In several families achlorhydria was associated with chronic diarrhoea, in one case through four generations. These authors conclude that pernicious anaemia is much more frequent than generally supposed and that the primary heredity factor is probably a diminution in the gastric secretory functions.

In a further study, Oliver and Wilkinson (1933) point out that absence of HCl in the gastric juice occurs after typhoid fever and in many other conditions. It can also arise as a constitutional condition present in many members of a family through several generations. It is associated not only with anaemia but also with allergy and with rheumatoid arthritis. While it may occur at any age, it is more common in later life. Moschcowitz (1931) reached similar conclusions regarding the relation of achlorhydria to pernicious anaemia and suggested that the latter represents a combination of a deficiency disease (perhaps lack of an unidentified member of the B complex) with lack of a gastric hormone.

Cooley (1941) also points out that achlorhydria is commonly present in families having pernicious anaemia and is often if not always a hereditary precursor of that disease. Lack of Castle's "intrinsic factor," an enzyme-like substance secreted by the stomach mucosa which controls the rate of red cell production in the bone marrow, is also apparently concerned. Ågren (1944) produces evidence that this "factor" is the enzyme amino-polypeptidase. Cooley finds that gastric cancer is frequent in families with pernicious anaemia. There are thus three conditions to be genetically accounted for: (1) those of the stomach, (2) those of the blood, (3) those of the spinal cord. One possible genetic interpretation is that these are three independent but closely linked genetic effects, but one pleiotropic gene may be concerned. It is also possible that macrocytic and microcytic anaemia are allelic mutations at the same locus of one chromosome.

In this connection may be cited a pedigree of Waugh (1935) in which hemolytic jaundice was present in seven persons in four generations, transmitted as a dominant. The cases of hemolytic jaundice had an olive complexion which was occasionally distinctly yellow, with yellow conjunctiva. The remarkable feature is that III. 2, having had hemolytic anaemia all his life and transmitted it to two of his children, developed pernicious anaemia at sixty-three, which was reduced again to hemolytic jaundice by liver therapy, with corresponding changes in the blood picture. During the pernicious stage both megaloblasts and microcytes were present in his blood. Perhaps the most likely explanation is that this man was heterozygous for both conditions, the pernicious anaemia developing late in life. If that is so, some of his four jaundiced ancestors, whose ages at death are not recorded, might also have been potential cases of pernicious anaemia, and the same of course applies to the son. This suggestion, however, is far from satisfactory and the whole matter of genetic relationships requires further investigations. Other similar cases have been reported.

Dogs can be made anaemic by bleeding or by injections of acetyl phenylhydrazine, but there has been failure so far to produce pernicious anaemia in animals.

Ranson and Reback (1942) record a case of pernicious anaemia which throws considerable light on the inheritance of this disease. They describe a man who, at the early age of twenty-two developed the disease together with degeneration of the spinal cord. His mother and his father's brother both had the same conditions. Perhaps the mother and uncle were both heterozygous for the condition, and the homozygous condition in the son brought on the disease at an extremely early age. The gene would be an irregular dominant, since it was not expressed in the father. As the disease sometimes occurs in successive generations, this seems the most likely interpretation.

Claussen (1939), in an analysis of *hemolytic anaemia*, concludes that it has a deep effect on bone growth, its prototype being hemolytic icterus. Weakness of the blood corpuscles leads to their increasing breakdown. This, in turn, in spite of greatly increased power of compensation of the bone marrow, results in lack of blood, jaundice, and hyperplasia of the spleen and liver where the red cells are manufactured. The hemolytic constitution appears to be a derangement of bone growth and of the blood-building marrow as the co-ordinated expression of a deep change in the system. Ovalocytosis, Naegeli's sphaerocytosis, sickle-cell anaemia and Cooley's erythroblastic anaemia with abnormal red cells and hyperostosis of the skull are all regarded as degrees of hemolytic anaemia with more or less marked tower skull.

Hypochromic Anaemia

This condition was defined by Faber in 1913, but was known much earlier under the name *chlorosis*. Dameshek (1931) shows the several respects in which it differs from pernicious anaemia. The individual shows pallor, sometimes from childhood, without icterus; atrophied tongue, spoon nails and achlorhydria. The red cells show hypochromia and are below the average in diameter. There is nevertheless hyperplasia of the bone marrow, which is crowded with erythroblasts and normoblasts. These cases respond not to liver but to iron and it is suggested that inadequate gastric digestion of organic iron is the primary condition. Seven cases were described, all but one females; they belonged to the northern nationalities generally, and brown eyes and hair were fully as common as blue eyes and fair hair. Mills (1931) simultaneously proposed for this condition the name *hypochromemia.* He described ten cases, all in women. Heredity was shown in one case where a daughter, aged fourteen years, was "decidedly chlorotic." Among several hundred cases of this disease now studied in Europe and America, only one was a male. This restriction to the female sex is another respect in which it differs from pernicious anaemia. Heath (1933) described three sisters who had symptoms of both pernicious and hypochromic anaemia with achlorhydria. Two brothers, a sister and the mother suffered from pernicious anaemia only, while two of the doubly affected daughters had a child with pernicious anaemia. This throws little light on the genetic relation between these two conditions.

Barrow (1934), in a summary of the literature, concludes that the hypochromic (achromic) anaemia with achlorhydria is frequently found in families where there is also primary or secondary anaemia in other members of the family.[10] He describes the case of a woman with the above type of anaemia whose mother and sister had a secondary anaemia of unknown origin.

Lundholm (1941) has explained the inheritance of hypochromic anaemia, which is next in frequency to pernicious anaemia. In Sweden it is particularly frequent in women after puberty and before the climacteric. Using Dahlberg's "later sibling's" method, Lundholm shows that it occurs among the sisters of patients with a frequency of 41 ± 6.6 per cent. Half the mothers also have the disease, which is dominant in women, with a penetrance of nearly 100 per cent. Lundholm's hypothesis is that the condition does not manifest itself unless there is loss of iron through bleeding. Normal persons quickly absorb the necessary iron in their food, but persons with this hereditary predisposition cannot do so. Women who have the gene develop anaemia and require large doses of iron because of loss of blood between the ages of fifteen and fifty. Men rarely suffer from it when no bleeding can be found, but the presence of the gene may be revealed if they have hemorrhoids, bleeding ulcer or wounds. Infections or lack of vitamins may reveal the condition in some men and women. The genic condition, which is transmitted as an ordinary dominant, then causes some abnormality in the digestive tract, giving *decreased power of absorbing iron. Loss of blood reveals the condition whenever present in the female but is only an exceptional occurrence in the male. Hence the disease is exhibited mainly in the female sex.*

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[10] Koilonychia is part of the syndrome of microcytic (hypochromic) anaemia, achlorhydria and glossitis, seen especially in middle-aged women.

Laufberger (1937) discovered the protein ferritin in horse spleen in the form of brown octahedral crystals containing 20 per cent iron. Granick and Michaelis (1943) removed the iron, producing colorless protein crystals (apoferritin) of the same form. They conclude that the iron in ferritin is in the form of colloidal micelles of $Fe(OH)_3$ filling the interstices of the crystal structure. They confirm Laufberger that ferritin functions as iron reserve in the body. Probably the inheritance element in hypochromic anaemia is the reduced ability to form ferritin.

Steiner (1939) described six cases of hypochromatic anaemia with blue sclera. These anomalies might be genetically or developmentally connected, or the blue color might be a result of disturbed iron metabolism.

Cooley (1945) has described a remarkable sublethal type of anaemia with elliptocytosis. The pedigree shows nineteen cases (all males) in five generations. There were ten normal brothers. Sixteen of the cases died, ten of them in their first year. The condition is either recessive sex-linked or possibly an autosomal gene dominant in males and recessive in females, like pattern baldness. There is, however, no case of transmission by an affected male. Two brothers in the fifth generation were studied. In both, the red cells tend to be microcytic and hypochromic, with periods of polycythemia, but the elder had no symptoms and may survive to reproduce.

Both mild and severe forms of hereditary anaemia have been studied in mice. A recessive form of anaemia due to inadequacy of the blood-forming cells is lethal in the homozygous condition (de Aberle, 1927). Before birth, the homozygous dominant whites are lighter in color, having only 25 per cent of the hemoglobin and 14 per cent of the red cells found in normals, and they die within ten days after birth. Individual tissues develop normally in tissue culture. The flexed-tailed mutation of the house mouse is also deficient in hemoglobin and erythrocytes at birth (Mixter and Hunt, 1933) but the defect disappears in about two weeks. This condition also appears to be recessive. Newborn mice are pale, but the condition is neither permanent nor fatal. It remained uncertain whether anaemia and flex tail are the pleiomorphic effects of a single gene or two genes closely linked.

Methemoglobinemia

In 1905 van den Bergh distinguished between cyanosis due to sulphhemoglobin and that due to methemoglobin. Both substances may be present in the blood at once. Dieckmann (1932) described a woman of twenty-seven whose skin had been blue from birth. She had tachycardia (rapid heart beat) and spectroscopic examination of her blood showed the presence of methemoglobin in large amounts. This is a chocolate-brown substance which cannot carry oxygen. It may be found in the blood of normal persons after large doses of acetanilid and other substances. Dieckmann found only six previous cases reported. Bensley, Rhea and Mills (1938) described the condition in a French-Canadian man of thirty-seven and his elder sister. He had a bluish discoloration of the skin from the age of twelve, his lips were blue and he suffered from constipation and periodic abdominal pain and vomiting. His sister had eight normal children. The condition is thus probably inherited as a rare Mendelian recessive.

Deeny, Murdock and Rogan (1943) describe the first cases of familial methemoglobinemia in the British Isles. A man of twenty-nine had a livid blue color from birth and a brother was less deeply cyanosed, his condition becoming pronounced at eleven years of age. The parents, two other brothers and a sister were normal. Unfortunately it is not stated whether the parents were related, but they cite a recent case in France and another in Austria with affected sibs, which increases the probability of recessive inheritance. In six sibships 10 ♂ and 4 ♀ children were affected, and perhaps one father. Graybiel *et al.* (1945) report the condition in a young man and his cousin, again indicating recessive inheritance. Both were blue babies. Some cases of cyanosis attributed to congenital heart disease are really of this origin. They cite a French case in which the inheritance is said to be dominant. Paul and Kemp (1944) find small amounts of methemoglobin normally present in the blood.

Felty's Syndrome

In 1924, Felty reported five cases of a condition in which chronic arthritis, splenomegaly and marked leukopenia were the symptoms. The patients were of both sexes and of middle age (forty-five to sixty-five). The symptoms resemble those of Still's disease except that the latter is found only in children, usually has increased leukocytes and a more severe form of arthritis. In a further study of the disease, Williams (1936) describes a case and summarizes the nine previous cases published. The uniformity of symptoms suggests that this is another inherited syndrome with its basis perhaps in a blood dyscrasia, but as yet only single cases have been reported.

High Blood Pressure

Hypertension, high blood pressure or hyperpiesia was recognized as hereditary even in the sixteenth century. Morgagni in 1769 recorded cases of apoplexy and found many similar cases among the relatives, leading to the belief that it was inherited. Dieulafoy (1876) cited from his experience ten families in which two to five members died of apoplexy in two or three generations. He regarded heredity as the factor of dominant importance in cerebral hemorrhage. All his cases, of which he cites at least thirty-one, were struck with hemiplegia with or without apoplexy. Some in an affected family were struck down at relatively early ages.

Gutmann (1927) described a remarkable pedigree of death by *apoplexy*. In five generations of a family of thirty-eight persons, fifteen died of apoplexy, five more have long had heart disease and obesity, and two others committed suicide. The inheritance is dominant, with only two skips. Again, in three closely related families in this village in Wurtemberg, since the middle of the eighteenth century eighty-two members have died of apoplexy.

Draper, Allen and Spock (1929) described a Russian Jewish family in which the mother died of cerebral hemorrhage. There were eight children. The eldest daughter, two sons and the three youngest daughters died from a stroke at the respective ages of *ca.* 60, *ca.* 60, 45, 55, 60 and 70. The other son and daughter developed high blood pressure and died of heart failure at *ca.* 45. The son of the eldest daughter also had high blood pressure.

Zipperlen (1932) confirmed the old observation that the pycnic man with apoplectic habitus is inclined to hypertension. His investigation of hypertonics in Tübingen showed a large excess of the pycnic type among those with constitutional high blood pressure; but in hypertension of nephrogenic origin (in which the kidneys are affected) there is a large number of leptosomics. The nephrogenic hypertonics frequently had chronic tonsillitis and were inclined to angina, which may be the hereditary component. In constitutional hypertension diabetes is relatively frequent as well as gall stones, obesity and rheumatism. A vasoneurosis was often present. Zipperlen described a family with 9 cases of hypertension (6♂ 3♀) in three generations, dominant, seven of which died of apoplexy. One grandmother suffered from dropsy.

Weitz (1936) made a detailed investigation of hypertensive disorders, with pedigrees, and concluded that, apart from dietary influences, the main causal element was heredity. Campbell (in Blacker, 1934) cited thirty cases of inherited heart disease associated with arteriosclerosis, obesity and hyperpiesia; in twenty-four the father or mother were affected, in six the parents were normal but the sibs of patients suffered. Hence it is usually dominant but sometimes either recessive or a dominant of irregular penetrance. In arteriosclerosis, heredity is regarded as more important than all other factors.

Herapath and Perry (1930) record a family in which the father and three sons died suddenly at early ages (thirty-one to forty-three years). There were two sons and three daughters unaffected. Premature senility of the coronary arteries was the cause. These arteries were found to be almost occluded, with intense vascularization of the left ventricle. The report is mentioned of an infant of seven weeks which died suddenly and was found to show advanced degenerative changes in the coronary arteries.

O'Hare, Walker and Vickers (1924) quote the case of a family in which ten of the twelve members had high blood pressure; another in which nine members died of apoplexy; and a third in which nine members have suffered from vascular disease in some form. They analyzed three hundred cases of permanent hypertension and found that 68 per cent of the relatives were affected. In a control series with non-vascular diseases the incidence of hypertension in relatives was only 37.6 per cent.

Weitz (1923) concluded that dominant inheritance accounts for most cases of genuine vascular hypertension. He studied the families of eighty-two affected persons. Death from heart disease or a "stroke" was much more frequent in their parents than in the general population and the parents seldom reached old age. Hypertension was also frequent in the siblings of hypertonics. After fifty-five, half the sibs had high tension or had already died of it. No more hypertension was found among alcoholics than others, and the idea that hypertension is generally connected with the pycnic and seldom with the asthenic type of constitution was not confirmed.

Coombs (1930) cites a family in which the father and four children all died of coronary disease. He mentions two cases of father and son with coronary infarction, and a third case of near relatives. Similarly there were families whose members all died of cerebral hemorrhage. Nine cases of *angina pectoris* in a family in four generations are shown in Fig. 239 after Boissevain (1931). In generation II all six members died of it, one at the early age of thirty. There is one skip in the third generation. Heberden gave the name angina pectoris in 1772, and the most accurate and complete account of the symptoms ever written, but without understanding the cause. He cited nearly a hundred cases, all but three in males, generally beginning after 50 years of age. Hamilton (1785) first referred to its inheritance.

Campbell (1934), in an account of hereditary cardiovascular diseases, cites some remarkable families with angina. A man of forty-four had it. His father, mother and first cousin died of it, another cousin had blood pressure over 200 and a third cousin dropped dead from coronary thrombosis. In another family the females were affected. A woman of forty-five had angina, her mother and sister died of heart disease, the maternal grandmother, cousin and aunt all died of angina. As the transmission is generally direct, a dominant inheritance is indicated. Von Verschuer (1934) described families in which *inflammation of the cardiac valves*, having a hereditary basis, is very frequent.

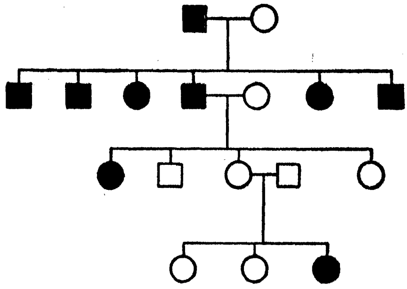

Fig. 239. Inheritance of angina pectoris. (After Boissevain)

Edmondson and Hoxie (1942) found in 25,000 autopsies in Los Angeles, 865 hearts with unhealed infarcts caused by coronary disease. Patients with hypertension which persists after infarction are three times more likely to develop cardiac rupture than those with normal or low blood pressure, but hypertrophy following infarction prevents rupture of the heart. Feldt and Wenstrand (1943) produce insurance examination statistics, based on 4376 cases, in which they find the incidence of familial cardiovascular disease only slightly greater among hypertensive persons than among those with normal blood pressure, and on this basis question the inheritance of hypertension.

Arteriosclerosis is one of the most frequent causes of death. It sometimes affects particular organs, producing several cases of cerebral hemorrhage or angina in a family. The manner of inheritance requires further investigation, but there may be an underlying dominant factor. Hueper (1944) has recently reviewed the subject of arteriosclerosis and related conditions, with full references.

Musser and Barton (1931) state that the Irish are relatively free from angina pectoris, probably because of an inherited racial disposition. They conclude that there are two types of coronary occlusion: (1) in elderly persons with general arteriosclerosis including that of the coronary system; (2) a familial condition generally in men not over sixty, with slight hypertension but no general arteriosclerosis.

In a Scottish family living in Bagdad, which numbered 108 individuals in five generations, Kennedy (1934) has given the causes of death so far as ascertained. Twenty-one died of cardiovascular disease and five cardiovascular patients were still living; five died of malignant tumors, one also having angina pectoris. The tuberculous numbered thirteen (four still living). Sixteen lived to over seventy and twelve more to over sixty years.

Allan (1933) points out that cardiovascular disease is so common that its frequent familial occurrence does not prove anything regarding its inheritance. He constructed tables showing the expected incidence of any unit trait in the parents, sibs and children of persons showing the trait, with incidences in the population ranging from 5 to 75 per cent. Apoplexy, sudden heart failure or congestive heart failure are all indications of high blood pressure, but clinical records of blood pressure date back only thirty years. The lower limit of hypertension is taken as 160 mm. mercury for systole and 100 mm. for diastole. From a statistical study of 480 patients one or both of whose parents had hypertension, it was concluded that the condition might be a simple dominant but the data were insufficient to prove it.

Ayman (1934) made a study of the height, weight and blood pressure of 1524 persons belonging to 277 families. He regarded 140 systolic, 80 diastolic as the lower limit for high blood pressure. On this basis, in the second generation he found 148 out of 780 children with hypertension at ages fourteen to thirty-nine years. These persons were 14.3 lb. above the average weight for normal children. In the families of parents with normal blood pressure only 3.1 per cent of the children had high blood pressure. When one parent had hypertension, 28.3 per cent of the children were in this condition, and when both parents were thus affected 45.5 per cent of the children were in the same condition. In eighteen families three generations were available and gave confirmatory results, showing the importance of the hereditary factor.

McFeeters (1941) records a pedigree, with twelve cases in three generations, of obesity with hypertension and cardiac disease. In some families the obesity begins early and in some late, but the high blood pressure is definitely dominant in inheritance, although alcohol, tobacco, work, mental and physical strain have all been assigned as causes. Weitz (1936) studied the causes of hypertension in the peasant population around Tübingen. He found the incidence of hypertension no higher in heavy drinkers than in the general population. Tobacco also had no appreciable effect on blood pressure, nor did excessive work or worry. Africans, Indians and Chinese suffer much less from hyperpiesia than Europeans and Americans, but when they adopt European diet their blood pressure rises. Hence the tendency to high blood pressure has a constitutional basis, but it may become manifest through faulty diet.

A family tendency to *arteriosclerosis* and to *angina pectoris* has been generally recognized for years. Goldsmith and Willius (1937) examined 300 cases (272 ♂ 28 ♀) in the Mayo Clinic and concluded that heredity plays a more important role in coronary disease than is generally admitted. Persons with *coronary thrombosis* were 6.7 per cent overweight for their height and age. Those with hypertension tended to be more overweight than those with normal blood pressure. In 165 of the 300 cases there was a family history of cardiovascular disease, but this showed no correlation with the degree of obesity.

Hines (1937) used a test. When the hand is immersed in ice water, normal persons show a minimal reaction, whereas in others there is a marked rise both in systolic and diastolic pressure. Among four hundred school children tested, 18.7 per cent were hyper-reactors although their blood pressure was normal. This condition is believed to precede hypertension. The inherited quality may then be a vasomotor system which reacts excessively to certain external and internal stimuli and so leads to the development of hypertension.

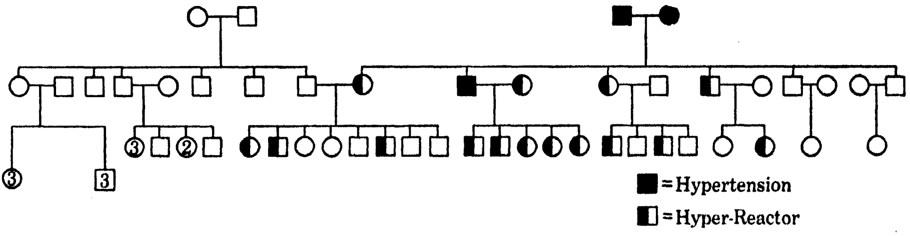

Fig. 240. Pedigree of hypertension and hyper-reactors. (After Hines)

The pedigree of one family is shown in Fig. 240. Hypertension appears to be inherited as a simple dominant. Thirty families with 256 members were subjected to the cold test and 12 of them gave only normal reactions, the other 18 showing a definite hypertensive diathesis. When both parents were normal in both respects none of the children were reactors. When both parents showed either hypertension or hyperreaction to cold 95 per cent of the children had one or the other condition (where 75 per cent would be expected). Where one parent was affected and the other not, 43.4 per cent of the children were hyper-reactors or had hypertension. Seven pairs of identical twins were concordant in their cold-reaction, while in two of three non-identical pairs the reactions were markedly different. There is thus evidence of a definite dominant factor, which may consist in an easily stimulated condition of the nerves controlling the dilation and contraction of the arteries and veins.

Schwab *et al.* (1935) had previously used the cold test for comparing the incidence of hypertensive cardiovascular disease in whites and negroes. The results indicate that a hypersensitive vasomotor mechanism is more frequent in negroes than whites. Since there is a higher incidence of cardiovascular disease in the negro (mainly due to syphilitic endarteritis), this may support the neurogenic concept of the development of this disease, i.e., that there is a primary constitutional factor as indicated by a hypersensitive vasomotor system. Some later results have supported Hines' conclusion that hyper-reactors later develop high blood pressure, but as numerous tests give contrary results (see Feldt and Wenstrand, 1942) the relationship is still doubtful. See also the discussion on hypertension in Bauer (1945).

Moschcowitz (1943) classes together hypertension, Graves' disease, peptic ulcer, cardiospasm, manic-depressive psychosis and paranoia, as hyperkinetic diseases arising in civilization. They are found, for example, in American but not in African Negroes, and cannot be produced experimentally in animals. He regards them as arising in five stages: (1) constitution (the genotype), (2) exaggeration of function, (3) a period of labile symptoms, (4) fixation of an exaggerated functioning, (5) somatic changes resulting from persistent exaggerated function. However, in examining hundreds of Melanesians in the New Hebrides and Solomons, Hyman (1945) found many with cardiovascular disturbances similar to those of civilization. One inter-related group showed hypertension, perhaps resulting from black-water fever and other infections. Another settlement had a number with hypotension. Coronary heart disease was common but was rarely accompanied by angina pectoris.

Hypotension

Although very little has been written on the subject, it is probable that low blood pressure is also inherited. Garvin (1927) published the case of a family in which six members — three brothers, two sisters and a son — all had low blood pressure, the values being 102 systolic, 70 diastolic, 96/70, 108/70, 94/72, 98/66 and 98/68. The condition is associated in this family with obesity. One of the women married into a family with hypertension. Her husband's pressure was 200/120, his sister 200/110; another sister and the mother died of a "stroke." The blood pressures of the children from this marriage would be of great interest. There is some evidence that low blood pressure is associated with long life. Whether constitutional racial differences in blood pressure exist is still being investigated (see also p. 1247). In the observations of Kean (1944) on the San Blas Indians, 408 between the ages of sixteen and sixty-six years were examined. The average systolic pressure was 105.2, diastolic 69.3, a large proportion showing marked hypotension.

A case is recorded (*Eugen. News* 17:99) in which *pulse rate* seems to be inherited, some children having a fast and some a slow pulse when the ancestors were some fast and some slow.

Hodgkin's Disease

Many views of this peculiar and invariably fatal disease have been expressed since its original description in 1832, but it is now regarded as essentially a blood disease, although little understood. It rarely occurs in children and frequently begins in adults with a glandular enlargement on one side of the neck, extending to the axillary, inguinal and mediastinal glands and the spleen (sometimes the liver), usually with a relapsing fever. The lymph glands contain fibroblasts, eosinophils and giant cells. It is a disease especially of the lymphatics and in one aspect is neoplastic (lymphogranulomatosis); in another aspect it may even be infectious in nature. Hodgkin's original paper described seven cases with splenic and lymphoid enlargement. Much later the effect on the bone marrow was recognized.

Krumbhaar (1931) describes a case with autopsy in which the disease was limited to the spleen and bone marrow. He suggests that it should be regarded as a disease of the hemolytopoietic (blood forming and blood destroying) or reticulo-endothelial system. Eosinophilia has long been regarded as an integral part of the histological picture. Stewart (1929) describes a case in which the count of eosinophilic leukocytes was extremely high in the blood as well as the bone marrow and the lymph nodes. His review of the subject shows that eosinophilia is frequently associated with allergic conditions of one kind or another. Longcope and McAlpin (1929) recognize five different forms of the disease. Apparently no familial cases have been described, which is not surprising if an infection as well as a neoplastic development of the lymph nodes and leukocytes is involved. An inherited constitutional background at least for Hodgkin's disease seems definitely indicated. Chambers (1943) reports that in tissue cultures from affected lymph nodes various bacteria and fungi which have been regarded as causative agents were sought for, with negative results, but some indication of virus inclusion bodies was found. In a distributional study of the disease in the United States, Hoster (1944) distinguishes between the granuloma and the sarcoma forms and cites the numerous causal organisms which have been suggested.

Myelogenic Osteopathy

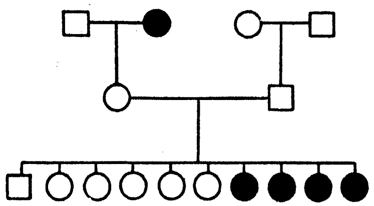

Fig. 241. Pedigree of myelogenic osteopathy. (After Markoff)

This term is applied to any bone-disease arising from impaired relation between the marrow and the osseous tissues. Markoff (1939) describes a family with five cases, all females, in three generations (Fig. 241). Marrow hyperplasia is the primary change. This disturbs the relation between marrow and bone. Osteomalacia follows on the basis of a constitutional defect in the mesenchyme.

Varicose Veins (*Phlebectasis*)

That heredity is a factor in the causation of phlebectasis or varicose (dilated) veins has long been recognized, but few cases have been examined from this point of view. Weber (1918) recognized so-called congenital varicose veins and congenital phlebarteriectasis and refers to various cases. In congenital phlebarteriectasis one extremity is longer than its mate. Probably both these conditions, as well as hemangiectatic hypertrophy of limbs, are inherited. Ottley (1934) studied the family incidence in fifty cases under treatment. Of these, fourteen knew of no other case in the family. In twenty-six families, however, the inheritance was that of a simple dominant, sometimes skipping a generation. The inherited condition is a weakness of the veins. One pedigree shows 14 cases (8♂ 6♀) in four generations. In certain families the inheritance might be recessive, but it is more probable that they were cases of irregular dominance.

Curtius (1928a) investigated some 1200 cases and recognized its dominant inheritance. The varicosis was regarded as a partial effect of general mesenchyme weakness, and statistical correlations indicated a general relation between varicosis and hernia. Curtius (1928b) examined nearly 4000 persons and concluded that leg varicosis is a simple dominant. He gives several pedigrees, the largest having 19 cases (8♂ 11♀) in four generations. When both parents are affected (two cases) all the eight children were affected. There is no case of skipping. In family II were 5 cases (3♂ 2♀) in four generations and family III showed 10 cases (7♂ 3♀) in four generations. Troisier and Le Bayon (1937) describe the inheritance of spontaneous phlebectasia, with pedigrees of 154 families (514 children). They find it a simple recessive, with 2♂:3♀ affected, and sex-linked in half the cases. The varicose veins appear during adolescence. When both parents were affected all the children were affected. There was no relation to eye color or hair color.

The inheritance of a serious tendency to the *breaking of blood vessels*, especially in the cavum nasi, is known in horses (Robertson, 1913). In the English thoroughbred racehorse there is a recessive gene which produces this result when present in the homozygous condition. The blood-coagulation is normal, but the blood-vessel walls must be fragile. The earliest known homozygous bleeder (not hemophilic) is the stallion Herod, born in 1748. The next famous racehorse "bleeder" was Hermit, who won the Derby in 1867, and was descended on both sides from Herod. Similarly Gallinule, born in 1884, was descended from Hermit. These all left numerous progeny. Humorist, who won the Derby in 1921, died seventeen days later from bleeding. Robertson found in the records 185 horses who were "bleeders," and 17 died from it. The recessive gene which is responsible for this condition must be widespread in racehorse stock, and must be considered as a semi-lethal in the homozygous state.

Thrombangiitis obliterans

This is a condition of gangrene, usually in the leg, following inflammation and clot formation in an artery or vein. It is also known as *Buerger's disease*, as he described it in 1908. There is seldom more than one case in a family, but a few families with several cases have been recorded. It is nearly always confined to the male sex, is associated with excessive cigarette smoking and has a predilection for Russian and Polish Jews. Toxins, nicotinism and ergotism have been ascribed as causes, also endocrine derangements and even cold. There appears to be a constitutional weakness of the endothelium of the arteries and veins, with greater viscosity of the blood. Averbuck and Silbert (1934) classify the cases of forty-seven patients who died following amputation for gangrene or from thromboses in the arteries of the heart, brain or intestines. It has been called *endophlebitis* and *gangrene of the feet.*

Mészáros (1931) described a Hungarian family with eight cases in two generations, but there is uncertainty about some of the cases, as four were women and no microscopic observations were made.

Samuels (1932), in a study of five hundred cases, found only three instances of its familial occurrence: (1) Three brothers were affected, whose parents were born in Austria. The eldest was thirty-four and began to smoke at fourteen years of age. (2) Three affected brothers were Russian Jews. (3) Two affected brothers were born in America of Austrian parents.

Weber and Huber (1939) present a case (Fig. 242) in which father and son were afflicted, the father (II. 1) finally having a leg amputated for gangrene. His father and his son's daughter suffered from asthma. The son (III. 3), whose right foot was affected, smoked ten cigarettes daily. The second pedigree shows thrombangiitis obliterans in the grandfather and Raynaud's disease, a related condition (*q.v.*) in the grandson. This family also had two cases of asthma, as well as three of diabetes. A constitutional factor is evidently involved, but its nature is obscure. Much use of tobacco, and apparently other external factors, can release the condition. The inherited diathesis appears to be recessive.

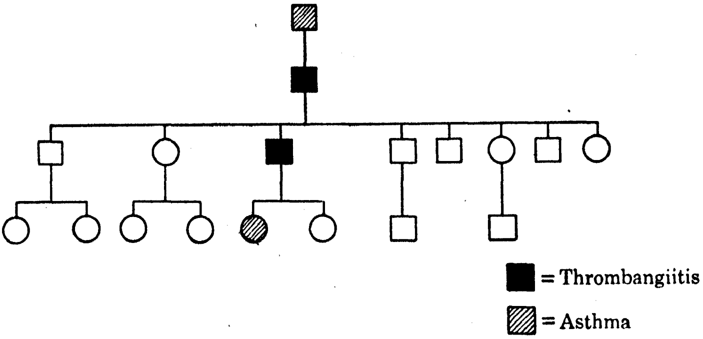

Fig. 242. Family pedigree showing thrombangiitis obliterans and asthma. (After Weber and Huber)

Reichert (1939) studied a family pedigree of two brothers both of whom had thrombangiitis obliterans, the collateral relatives having three cases of rheumatoid arthritis, two of rheumatic trouble, six of susceptibility to infection, three of mesenchymal defect, one of disease of the circulation and one of allergy. This accumulation of rheumatic and other diseases leads to the conclusion that in thrombangiitis obliterans, besides defective development of the connective tissue as a determining component is a susceptibility of the circulatory system. Thompson (1944), in an extensive study, regards post-phlebitic ulcers and thrombangiitis obliterans as related conditions. Their etiology is still obscure, but allergic sensitivity resulting from skin infection by certain fungal dermatophytes is regarded as an important factor.

Silbert (1945) studied over 1400 cases. One hundred stopped smoking and were observed for ten years. The disease was completely arrested in all. He concludes that it is caused by smoking in persons who are constitutionally sensitive to tobacco. This disease is supposed to be rare in Negroes, but Yater (1937) made a pathological study of five cases in males believed to be of full blood. Two were excessive cigarette smokers and three moderate smokers.

LITERATURE

de Aberle, S. B. 1927. A study of the hereditary anemia of mice. *Am. J. Anat.* 40:219–247. Pl. 1.

Ågren, G. 1944. Nature of the anti-anaemic factor (Castle). *Nature* 154:430–431.

Allan, Wm. 1933. Heredity in hypertension. *Arch. Int. Med.* 52:954–958.

Apley, J. & Grant, G. H. 1945. Tropical eosinophilia as seen in England. *Lancet* 248:812–813.

Archibald, R. G. 1926. A case of sickle cell anaemia in the Sudan. *Trans. Roy. Soc. Trop. Med. & Hyg.* 19:389–393. Figs. 4.

Armand-Delille, P. F., Hurst, A. F. & Sorapure, V. E. 1930. Familial eosinophilia. *Guy's Hosp. Repts.* 10:248–252.

Arneth, J. 1937. Über die qualitativen Blutbefunde bei der "Pelgerschen Kernanomalie der Leukocyten." *Fol. Haem.* 57:353–388.

Askey, J. M. 1940. Prevention of pernicious anemia: recognition of the latent stage. *Ann. Int. Med.* 14:593–607.

Atkinson, Dorothy W. 1939. Erythroblastic anemia. *Am. J. Med. Sci.* 198:376–383. Pls. 2.

Averbuck, S. H. & Silbert, S. 1934. Thrombo-angiitis obliterans. *Arch. Int. Med.* 54:436–465.

Ayman, D. 1934. Heredity in arteriolar (essential) hypertension. *Arch. Int. Med.* 53:792–802.

Barrow, W. H. 1934. The hereditary and familial factor in hypochromic anemia with achlorhydria. *Ann. Int. Med.* 7:1135–1140.

Bastai, P. 1923. Della eosinofilia constituzionale. *Haematologica* 4:23–58.

Beckman, T. M. & Jäderholm, K. B. 1932. Contribution to the knowledge of familial hemolytic icterus in Sweden with particular reference to results of operation. *Acta Chir. Scand.* 69:353–377.

Bensley, E. H., Rhea, L. J. & Mills, E. S. 1938. Familial idiopathic methaemoglobinaemia. *Quart. J. Med.* 31:325–330.

van den Bergh, A. A. H. 1931. On elliptic red blood-corpuscles (ovalocytosis). *Proc. Kon. Neder. Akad. Wetens.* 34:749–754.

———. 1931a. A propos des hématies elliptiques (l'ovalocytose). *Rev. Belge de Sci. Med.* 3:683–688.

Bezançon, F. & Moreau, R. 1914. L'eosinophilie dans les diathèses et les états anaphylactiques. *Ann. de Med.* 2:85–102.

Bishop, F. W. 1914. Elliptical human erythrocytes. *Arch. Int. Med.* 14:388–392. Figs. 4.

Boissevain, Ethel. 1931. The inheritance of angina pectoris. *Eugen. News* 16:115.

Bramwell, B. 1916. Familial cirrhosis of the liver. *Edinb. Med. J.* 17:90–99.

Brockmann, H. 1937. Untersuchungen über die Erblichkeit der Polycythaemia vera rubra. *Zeits. f. Vererb. u. Konst-lehre* 20:380–458.

Burks, Barbara S. & Wyandt, Helen. 1941. Oval blood cells in human subjects tested for linkage with taste for PTC, mid-digital hair, hair color, A–B agglutinogens, and sex. *Genetics* 26:223–233.

Caminopetros, J. 1938. Recherches sur l'anémie erythroblastique infantile, des peuples de la Mediterranée orientale. *Ann. de Med.* 43:27–61, 104–125. Figs. 20.

Campbell, J. M. H. & Warner, E. C. 1926. Heredity in acholuric jaundice. *Quart. J. Med.* 19:333–355. Figs. 2.

Campbell, M. 1934. In Blacker, *The Chances of Morbid Inheritance* London. Pp. 246–279.

Canby, C. B., Carpenter, G. & Ellmore, L. F. 1944. Drepanocytosis (sicklemia) and an apparently acute surgical condition of the abdomen. *Arch. of Surgery* 48:123–125.

Casey, A. E., Rosahn, P. D., Hu, C. K. & Pearce, L. 1934. Hereditary variations in the blood cytology of normal rabbits. *Science* 79:189–190.

*César, H. B. 1943. (Familial chronic malignant neutropenia with atypical granulations of the leukocytes.) *Bol. Soc. Cubana de Pediatria.* 15:900.

Chambers, R. 1943. *Rept. of Internat. Res. Foundn.* P. 39.

Cheney, G. 1932. Elliptic human erythrocytes. *J. Amer. Med. Assn.* 98:878–881. Figs. 3.

Cheney, W. F. & Cheney, G. 1934. Chronic hereditary hemolytic jaundice. *Am. J. Med. Sci.* 187:191–213.

Cirio, L. 1926. Sopra un caso di cosidetta eosinofilia constituzionale. *Riforma Med.* 42:219–222.

Claussen, F. 1939. Phänogenetik vom Menschen. *Zeits. f. Abst. u. Vererb.* 76:14–46. Figs. 16.

Collis, W. R. F. 1934. Icterus gravis neonatorum. *Irish J. Med. Sci.* No. 99, 106–112.

Connor, H. M. 1930. Hereditary aspect of achlorhydria in pernicious anemia. *J. Am. Med. Assn.* 94:606–612.

Cooke, W. E. & Hill, C. F. 1930. Microscopical studies in pernicious anaemia. *J. Roy. Micro. Soc.* 50:427–431. Pls. 2.

Cooley, T. B. 1928. Likenesses and contrasts in the hemolytic anemias of childhood. *Am. J. Dis. Child.* 36:1257–1262.

———. 1941. Hereditary factors in the blood dyscrasias. *Am. J. Dis. Child.* 62:1–8.

———. 1945. A severe type of hereditary anemia with elliptocytosis. *Am. J. Med. Sci.* 209:561–568. Figs. 4.

Cooley, T. B. & Lee, Pearl. 1929. Sickle cell anemia in a Greek family. *Am. J. Dis. Child.* 38:103–106. Figs. 2.

Cooley, T. B., Witwer, E. R. & Lee, Pearl. 1927. Anemia in children, with splenomegaly and peculiar changes in the bones. *Am. J. Dis. Child.* 34:347–363. Figs. 8.

Coombs, C. F. 1930. Observations on the aetiological correspondence between anginal pains and cardiac infarction. *Quart. J. Med.* 23:233–239.

Cooper, E. L. 1941. Familial acholuric jaundice associated with bone changes. *Ann. Int. Med.* 15:858–868. Figs. 6.

Cowen, S. O. 1936. Treatment of familial acholuric jaundice. *Brit. Med. J.* i. 690–692.

Cremer, J. 1941. Vergleichende Untersuchungen zum Feltyschen Syndrom. *Deut. Arch. Klin. Med.* 187:269–280. Figs. 5.

Curtius, F. 1928a. Die Vererbung der menschlichen Phlebektasien. *Verh. V. Internat. Kongr. Vererb.* i. 576–577.

———. 1928b. Untersuchungen über das menschliche Venensystem I. Die hereditäre Ätiologie der Bein-Phlebectasien. *Deut. Arch. Klin. Med.* 162:194–214.

Dacie, J. V. & Gilpin, A. 1944. Refractory anaemia (Fanconi type). *Arch. of Dis. Child.* 19:155–162.

Dameshek, W. 1931. Primary hypochromic anemia (erythronormoblastic anemia). *Am. J. Med. Sci.* 182:520–553. Figs. 3.

———. 1943. Familial Mediterranean target-oval cell syndromes. *Am. J. Med. Sci.* 205:643–660. Figs. 6.

Dameshek, D. & Singer, K. 1941. Familial nonhemolytic jaundice. *Arch. Int. Med.* 67:259–285. Figs. 5.

Davis, L. J. 1944. Macrocytic anaemia in children. *Arch. of Dis. Child.* 19:147–154. Figs. 2.

Dawson of Penn, Lord. 1931. Haemolytic icterus. *Brit. Med. J.* i. 921–928, 963–966. Col. pls. 2, figs. 6.

Debré, R. 1939. Familial hepatitis and chronic jaundice. *Lancet* 236:760–761.

———. 1939. Familial hepatitis and chronic jaundice. *Proc. Roy. Soc. Med.* 32:1173–1184.

Deeny, J., Murdock, E. T. & Rogan, J. J. 1943. Familial idiopathic methaemoglobinaemia. *Brit. Med. J.* i. 721–723.

Dieckmann, W. J. 1932. Methemoglobinemia. *Arch. Int. Med.* 50:574–578.

Dieulafoy, M. 1876. Du rôle de l'hérédite dans la production de l'hémorrhage cérébrale. *Gaz. hebd. de Méd.* 13:595–597.

Diggs, L. W., Ahmann, C. F. & Bibb, J. 1933. The incidence and significance of the sickle cell trait. *Ann. Int. Med.* 7:769–778.

Diwani, M. 1944. Erythroblastic anaemia with bone changes in Egyptian children. *Arch. of Dis. Child.* 19:163–168. Figs. 11.

Doll. 1926. Über familiären hämolytischen Ikterus (familiäre hämolytische Anämie). *Mitt. Grenzgeb. Med. u. Chir.* 40:12–33.

Draper, G., Allen, G. & Spock, J. C. 1929. Studies in human constitution. VI. Clinical genetics. *J. Am. Med. Assn.* 92:2148–2153.

Dresbach, M. 1904. Elliptical human red corpuscles. *Science* 19:469–470; 21:473–475.

Drew, J. H. & Grant, F. C. 1945. Polycythemia as a neurosurgical problem. *Arch. of Neur. & Psychiat.* 54:25–36. Figs. 5.

Duran-Jorda, F. 1943. Formation of red blood corpuscles. *Lancet* 244:513–514. Figs. 5. 245:186–188. Figs. 8.

Edmondson, H. A. & Hoxie, H. J. 1942. Hypertension and cardiac rupture. *Amer. Heart J.* 24:719–733. Figs. 4.

Engelking, E. 1920. Ueber familiäre Polycythaemie und die dabei beobachteten Augenveränderungen. *Klin. Monatsbl. f. Augenhlk.* 64:645–664.

English, R. B. 1943. A note on the occurrence of the sickle-cell trait in the blood of a Bantu. *S. Afr. Med. J.* 17:389–390.

Evans, R. M. 1941. T.N.T. jaundice. *Lancet* 24:552–554.

Evans, R. W. 1944. The sickling phenomenon in the blood of West African natives. *Proc. Roy. Soc. Trop. Med.* 37:281–286. Fig. 1.

*Fanton, E. 1928. Contributo alla studio della cosidetta diatesi eosinofilia. *Clin. Pediat.* 10:295–306.

Fawdry, A. L. 1944. Erythroblastic anaemia of childhood (Cooley's anaemia) in Cyprus. *Lancet* 246:171–176. Figs. 2.

Feldt, R. H. & Wenstrand, D. E. W. 1942. The cold-pressor test in subjects with normal blood pressure. *Am. Heart J.* 23:766–771.

———————. 1943. The family history in arterial hypertension. *Am. J. Med. Sci.* 205:61–65.

Felty, A. R. 1924. Chronic arthritis in the adult, associated with splenomegaly and leukopenia. *Bull. Johns Hopkins Hosp.* 35:16–20.

Fitz, R., Walker, B. S. & Branch, C. F. 1942. Polycythaemia vera. *Arch. Int. Med.* 70:919–934. Figs. 7.

Fordyce, A. D. & McFee, W. G. 1924. The tendency of the newborn to jaundice. *Lancet i.*1151–1153.

Frank, H. 1933. Erblichkeit der Anaemia perniciosa und Beobachtung an eineiigen Zwillingen. *Deut. Arch. Klin. Med.* 175:96–107. Figs. 4.

Friedlander, R. D. 1934. The racial factor in pernicious anemia. *Am. J. Med. Sci.* 187:634–642.

Garvin, J. D. 1927. Hypotension. *J. Am. Med. Assn.* 88:1875–1876.

Gillespie, W. A. 1943. The influence of lysolecithin and of incubation on the shape, size and fragility of erythrocytes. *Quart. J. Exp. Physiol.* 32:113–120.

Glazebrook, A. J. 1944. Koilonychia and polycythaemia vera. *Edinb. Med. J.* 51:65–69.

Goldsmith, G. A. & Willius, F. A. 1937. Bodily build and heredity in coronary thrombosis. *Ann. Int. Med.* 10:1181–1186.

Gram, H. C. 1930. Further observations on a family showing many cases of pernicious anemia. *Acta Med. Scand. Suppt.* 34:107–113.

Granick, S. & Michaelis, L. 1943. Apoferritin of horse spleen. *J. Biol. Chem.* 147:91–97.

Graybiel, A., Lilienthal, J. L., Jr. & Riley, R. L. 1945. The report of a case of idiopathic congenital (and probably familial) methemoglobinemia. *Bull. Johns Hopkins Hosp.* 76:155–162. Fig. 1.

Greenwald, L. & Burrett, J. B. 1940. Sickle-cell anemia in a white family. *Am. J. Med. Sci.* 199:768–774. Pl. 1.

Greenwald, L. Spielholz, J. B. & Litwins, J. 1943. Sickling trait in a white adult associated with hemolytic anemia, endocarditis and malignancy. *Am. J. Med. Sci.* 206:158–168. Figs. 6.

Grüneberg, H. 1939. Inherited macrocytic anemias in the house mouse. *Genetics* 24:777–810.

Grzegorzewski, H. 1933. Über familiäres Vorkommen elliptischer Erythrocyten beim Menschen. *Folia Haem.* 50:260–277. Figs. 7.

Gunn, C. H. 1938. Hereditary acholuric jaundice in a new mutant strain of rats. *J. Hered.* 29:137–139.

———. 1944. Hereditary acholuric jaundice in the rat. *Can. Med. Assn. J.* 50:230–237. Figs. 3.

Gutmann, M. J. 1927. Zum familiären Vorkommen des Schlaganfalls. *Arch. f. Rass. u. Ges.-Biol.* 20:70–71.

Haden, R. L. 1934. The mechanism of the increased fragility of the erythrocytes in congenital hemolytic jaundice. *Am. J. Med. Sci.* 188:441–449.

Haden, R. L. & Evans, F. D. 1937. Sickle cell anemia in the white race. *Arch. Int. Med.* 60:133–142. Figs. 3.

*Hamilton, R. 1785. *Medical Commentaries.* London.

Hansen, K. & Klein, E. 1934. Über Symptomatologie und Vererbung des hämolytischen Ikterus (Kugelzellanämie). *Deut. Arch. f. Klin. Med.* 176:567–580.

Hawksley, J. C. & Lightwood, R. 1934. A contribution to the study of erythroblastosis: icterus gravis neonatorum. *Quart. J. Med.* 27:155–209. Pls. 5.

Heath, C. W. 1933. The interrelation of pernicious anemia and idiopathic hypochromic anemia. *Am. J. Med. Sci.* 185:365–381. Figs. 4.

Herapath, C. E. K. & Perry, C. B. 1930. The coronary arteries in a case of familial liability to sudden death. *Brit. Med. J.* i. 685–687. Figs. 7.

Herrick, J. B. 1910. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. *Arch. Int. Med.* 6:517–521. Figs. 4.

Hines, E. A., Jr. 1937. The hereditary factor in essential hypertension. *Ann. Int. Med.* 11:593–601.

Hittmair, A. & Auhuber, M. 1930. Icterus hemolyticus bezw. familiäre hämolytische Anämie mit besonderer Berücksichtigung der Blutgruppenvererbung. *Fol. Haem.* 42:80–90.

Hodgkin, Dr. 1832. On some morbid appearances of the absorbent glands and spleen. *Medico-Chirur. Trans.* 17:68–114.

Hoster, H. A. 1944. A distribution study of Hodgkin's disease in the United States. *Ohio J. Sci.* 44:245–251.

Huber, H. 1939. Stammbaumuntersuchungen bei Panmyelophthisekranken. *Klin. Woch.* 18:1145–1150.

Hueper, W. C. 1944. Arteriosclerosis. *Arch. of Pathol.* 38:162–181, 245–285.

Huët, G. J. 1932. Über eine bisher unbekannte familiäre Anomalie der Leukocyten. *Klin. Wochen.* 11:1264–1266.

Hunter, W. C. 1932. A further study of a white family showing elliptical erythrocytes. *Ann. Int. Med.* 6:775–781.

Hunter, W. C. & Adams, R. B. 1929. Hematologic study of three generations of a white family showing elliptical erythrocytes. *Ann. Int. Med.* 2:1162–1174.

Hyman, A. S. 1945. Heart disease in the jungles of the South Pacific. *Ann. Int. Med.* 22:639–652.

Iwao, T. & Yoshida, T. 1940. Ein allererster Fall von Elliptoerythrocytose in Japan. *Folia Haematol.* 63:471–477. Figs. 9.

Japa, J. 1945. A study of haemopoiesis in pernicious anaemia bone marrow. *Brit. J. Exp. Path.* 26:111–120. Figs. 2.

Kean, B. H. 1944. The blood pressure of the Cuna Indians. *Am. J. Trop. Med.* 24:341–343. Fig. 1.

Kennedy, W. P. 1934. Morbidity in a family tree. *Brit. Med. J.* ii. 630–631. Ueber familiäre (erbliche) Eosinophilie.

Klinkert, D. 1911. Über familiäre (erbliche) Eosinophilie. *Berl. Klin. Wochens.* 48:938–939.

———. 1920. Das Problem der konstitutionellen Eosinophilie. *Zeit. Klin. Med.* 89:156–171.

Knoll, W. 1930. Das Blutbild der Cameliden. *Fol. Haem.* 42:350–358. Figs. 11.

Koch, L. A. & Shapiro, B. 1932. Erythroblastic anemia. *Am. J. Dis. Child.* 44:318–335. Figs. 8.

Koenan, O. 1938. Ein Familienstammbaum von hämolytischem Ikterus. *Zeits. f. Klin. Med.* 135:115–122.

Krumbhaar, E. B. 1931. Hodgkin's disease of the bone marrow and spleen without apparent involvement of lymph nodes. *Am. J. Med. Sci.* 182:764–769. Figs. 4.

LaCour, L. F. 1944. Mitosis and cell differentiation in the blood. *Proc. Roy. Soc. Edinb.* 62B:73–85. Figs. 5, Pls. 3.

Laufberger, V. 1937. Sur la cristallisation de la ferritine. *Bull. Soc. Chim. Biol.* 19:1575–1582.

Lawrence, J. S. 1931. Human elliptical erythrocytes. *Am. J. Med. Sci.* 181:240–245. Figs. 5.

Leitner, St. J. 1938. Weitere Untersuchungen über die Pelger-Huëtsche familiäre Kernanomalie der Leukocyten. *Fol. Haem.* 60:329–364. Figs. 10.

———. 1943. Weitere Untersuchungen über die familiäre Elliptozytose der Erthrozyten. *Helvet. Med. Acta* 10:583–603. Figs. 4.

Leitner, St. J. & van Leeuwen, J. J. 1935. Die Pelger-Huëtsche familiäre Kernanomalie der Leukocyten. *Klin. Wochens.* 14:17–19.

Levine, P., Burnham, L. *et al.* 1941. The role of iso-immunization in the pathogenesis of erythroblastosis fetalis. *Am. J. Obst. & Gynec.* 42:925–937.

Levy, J. 1929. Sicklemia. *Ann. Int. Med.* 3:47–54.

Lieberherr, W. 1938. Ueber Ovalocytose. *Helvet. Med. Acta* 5:589–596.

Lightwood, R. & Hawksley, J. C. 1933. *Proc. Roy. Soc. Med.* 26:1368–1372; 27:255–257.

Lloyd, T. W. 1941. On the aetiology of acholuric family jaundice. M. D. Thesis, Oxford. Pp. 51.

Longcope, W. T. & McAlpin, K. R. 1929. Hodgkin's disease. *Oxford Medicine* 4:1–43.

Lundholm, I. 1941. Inheritance of hypochromic anemia. *Proc. 7th Internat. Genet. Congr.* 198–199.

McCarty, S. H. 1933. Elliptical red blood cells in man. *J. Lab. & Clin. Med.* 19:612–621. Figs. 6.

McFeeters, J. W. 1941. A study of heredity in an isolated village community. *Eugen. Rev.* 33:73–80.

McGavack, T. H. & German, W. M. 1944. Sicklemia in the black Carib Indian. *Am. J. Med. Sci.* 208:350–355. Fig. 1.

Maclachlan, W. W. G. & Kline, F. M. 1926. The occurrence of anemia in four generations. *Am. J. Med. Sci.* 172:533–543.

Mandelbaum, H. 1939. Report of a case of congenital hemolytic jaundice. *Ann. Int. Med.* 13:872–883.

Manson, J. S. 1928. *Observations on human heredity.* London: Lewis. Pp. 84, pls. 8, figs. 19.

Markoff, N. 1939. Die myelogene Osteopathie. *Fol. Haemat.* 62:337–366. Col. pl. 1, figs. 24.

Martinez, F. F. 1927. Les achylies gastriques familiales. *Paris Méd.* 65:85–90.

Mészáros, K. 1931. Arteriitis obliterans (Thromboangiitis Buerger) als familiäre Erkrankung. *Deut. Arch. Klin. Med.* 171:391–396.

Meulengracht, E. 1922. *Der chronische hereditäre hämolytische Ikterus.* Leipzig: Klinkhardt. Pp. 226, pls. 5.

———. 1925. The hereditary factor in pernicious anemia. *Am. J. Med. Sci.* 169:177–195.

Mills, E. S. 1931. Idiopathic hypochromemia. *Am. J. Med. Sci.* 182:554–565.

———. 1938. Thalassanemia, report of a case. *Arch. Int. Med.* 62:1004–1014. Figs. 5.

Minkowski, O. 1900. *Verhandl. d. Kongr. f. inn. Med. Wiesbaden* 18:316–319.

Mixter, R. & Hunt, H. R. 1933. Anemia in the flexed tail mouse, *Mus musculus. Genetics* 18:367–387.

Moncrieff, A. & Whitby, L. E. H. 1934. Cooley's anaemia. *Lancet* 227:648–649.

Moschcowitz, E. 1931. The relation of achlorhydria to pernicious anemia. *Arch. Int. Med.* 48:171–186.

———. 1943. The hyperkinetic diseases. *Am. J. Med. Sci.* 206:576–599.

Murphy, R. C. & Shapiro, S. 1944. Observations on behavior of erythrocytes in sickle cell disease. *Arch. Int. Med.* 74:28–35.

——— ———. 1945. The pathology of sickle cell disease. *Ann. Int. Med.* 23:376–397. Figs. 6.

Musser, J. H. & Barton, J. C. 1931. The familial tendency of coronary disease. *Am. Heart J.* 7:45–51.

Mustelin, O. 1922. Erblichkeit und perniziöse Anämie. *Acta Med. Scand.* 56:411–418.

Nadler, S. B. & Cohn, I. 1939. Familial polycythemia. *Am. J. Med. Sci.* 198:41–48.

Neel, J. V. & Valentine, W. N. 1945. The frequency of thalassemia. *Am. J. Med. Sci.* 209:568–572.

O'Hare, J. P., Walker, W. G. & Vickers, M. C. 1924. Heredity and hypertension. *J. Am. Med. Assn.* 83:27–28.

Oliver, T. H. & Wilkinson, J. F. 1933. Achlorhydria. *Quart. J. Med.* 26:431–462.

Ottley, Constance. 1934. Heredity and varicose veins. *Brit. Med. J.* i. 528.

Pache, H. D. 1939. Die erbliche Form der Neugeborenenerythroblastose II. *Zeits. f. Kinderhlk.* 61:86–91.

Palma, M. D. 1931. Sulla eosinofilia famigliare. *Policlinico (Sez. Med.)* 38:605–619. Pl. 1.

Parsons, F. B. 1939. Familial hepatitis. *Proc. Roy. Soc. Med.* 32:1197–1199.

Paul, W. D. & Kemp, C. R. 1944. Methemoglobin: a normal constituent of the blood. *Proc. Soc. Exp. Biol. Med.* 56:55–56.

*Pelger. 1928. Nederl. Ziektekundige Vereeniging (cited by Zündel).

Penfold, J. B. & Lipscomb, J. M. 1943. Elliptocytosis in man associated with hereditary haemorrhagic telangiectasia. *Quart. J. Med.* 12:157–167. Figs. 4.

Piney, A. 1925. The genesis of pernicious anaemia. *Zeits. f. Konst-lehre* 10:659–685.

Pollock, L. H. & Dameshek, W. 1934. Elongation of the red blood cells in a Jewish family. *Am. J. Med. Sci.* 188:822–834.

Ponder, Eric. 1941. Structure of the red cell in the light of shape transformations. *Collecting Net* 16:101–107.

———. 1942. Quantitative aspects of the disk space transformation produced by lecithin. *J. Exp. Biol.* 19:220–231. Fig. 1.

———. 1945. The sickling phenomenon and its bearing on the problem of red cell structure. *J. Exp. Biol.* 21:77–83. Fig. 1.

Race, R. R. 1942. On the inheritance and linkage relations of acholuric jaundice. *Ann. Eugen.* 11:365–384.

Ranson, S. W., Jr. & Reback, S. 1942. A case of subacute combined degeneration of the spinal cord with interesting hereditary features. *Ann. Int. Med.* 17:738–744.

Reichert, O. 1939. Erbbedingtheit der Thrombangiitis obliterans. Beitrag zum Erbgang beim Rheumatismus. *Zeits. f. Vererb. u. Konst.* 23: 53–66.

Reid, J. T., Huffman, C. F. & Duncan, C. W. 1945. Poikilocytosis in dairy cattle. *Arch. of Pathol.* 39:351–357. Figs. 3.

Roberts, J. A. F. 1945. Genetic linkage in man, with particular reference to the usefulness of very small bodies of data. *Quart. J. Med.* 14:27–33.

Robertson, J. B. 1913. The heredity of bloodvessel breaking in the thoroughbred. *Bloodstock Breeders' Rev.* 2:265–281.

Rosenfeld, S. & Pincus, J. B. 1932. The occurrence of sicklemia in the white race. *Am. J. Med. Sci.* 184:674–682. Figs. 2.

Rotter, W. 1933. Elliptische rote Blutkörperchen als familiär vererbbare Anomalie. *Klin. Wochens.* 12:1777.

Ryerson, C. S. & Terplan, K. L. 1935. Sickle cell anemia. Two unusual cases with autopsy. *Fol. Haemat.* 53:353–369. Figs. 10.

Samuels, S. S. 1932. The incidence of thrombo-angiitis-obliterans in brothers. *Am. J. Med. Sci.* 183:465–467.

Sar, A. van der. 1944. The Pelger-Huëts' familiar nuclear anomaly of the leucocytes. *Am. J. Clin. Pathol.* 14:544–548. Figs. 8.

Schemm, F. R. 1940. A pernicious anemia family. *Am. J. Med. Sci.* 199:167–171.

Schinz, H. R. 1943. Erbgang bei Pelger Anomalie. *Praxis* (Berne) 32:730–731. Fig. 1.

Schrumpf, C. A. A. 1935. Ein Fall von familiärer Cholämie. *Klin. Wochens.* 14:612–613.

Schwab, E. H. *et al.* 1935. Blood pressure response to a standard stimulus in the white and negro races. *Proc. Soc. Exp. Biol. & Med.* 32:583–585.

Schwartz, S. O. 1945. The prognostic value of marrow eosinophils in thrombocytic purpura. *Am. J. Med. Sci.* 209:579–587.

Scriver, J. B. & Waugh, T. R. 1930. Studies on a case of sickle-cell anaemia. *Canad. Med. Assn. J.* 23:375–380.

Sights, W. P. & Simon, S. D. 1931. Marked erythrocyte sickling in a white adult, associated with anemia, syphilis and malaria. *J. Med.* 12:177–178.

Silbert, S. 1945. Etiology of thrombangiitis obliterans. *J. Am. Med. Assn.* 129:5–9.

Singer, K. 1933. Myositis und Eosinophilia. *Deut. Arch. Klin. Med.* 175:281–290. Fig. 1.

Smith, C. H. 1943. Familial blood studies in cases of Mediterranean (Cooley's) anemia. *Am. J. Dis. Ch.* 65:681–701. Figs. 6.

Spodaro, A. & Forkner, C. E. 1933. Benign familial polycythemia. *Arch. Int. Med.* 52:593–602.

Stamos, H. F. 1940. Heredity in pernicious anemia. *Am. J. Med. Sci.* 200:586–590.

Steinbrinck, W. & Hahnelt. 1938. Über familiäre Ovalozytose. *Deut. Med. Wochens.* 64:784–785. Fig. 1.

Steiner, F. 1939. Konstitutionelle hypochrome Anämien mit Blaufärbung der Skleren. *Zeits. f. Vererb. u. Konst.* 23:484–490.

Stewart, S. G. 1929. Eosinophilic hyperleukocytosis in Hodgkin's disease with familial eosinophilic diathesis. *Arch. Int. Med.* 44:772–783. Figs. 6.

———. 1933. Familial eosinophilia. *Am. J. Med. Sci.* 185:21–29.

Strauss, M. B., Daland, G. A. & Fox, H. J. 1941. Familial microcytic anemia. *Am. J. Med. Sci.* 201:30–34. Figs. 2.

Sydenstricker, V. P. 1923. Elliptic human erythrocytes. *J. Am. Med. Assn.* 81:113–114. Figs. 2.

Terry, M. C., Hollingsworth, E. W. & Eugenio, V. 1932. Elliptical human erythrocytes. *Arch. of Pathol.* 13:193–206.

Thompson, K. W. 1944. Studies on the relationship of dermatomycosis to ulceration and gangrene of the extremities. *Yale J. Biol. & Med.* 16:665–753. Figs. 24.

Tileston, W. 1922. Hemolytic jaundice. *Medicine* 1:355–388.

Tinney, W. S., Polley, H. F., Hall, B. E. & Giffin, H. Z. 1945. Polycythemia vera and gout. *Proc. Mayo Clinic* 20:49–55.

Tischendorf, W. 1939. Zwei weitere Familien mit Pelgersche Kernanomalie. *Folia Haem.* 62:254–260. Figs. 3.

Tomlinson, W. J. 1941. Studies on sicklemia blood, with a new method for its rapid diagnosis. *Am. J. Clin. Pathol.* 11:835.

———. 1945. The incidence of sicklemia and sickle cell anemia in 3000 Canal Zone examinations upon natives of Central America. *Am. J. Med. Sci.* 209:181–186.

Towle, R. A., Coulson, F. H. & Fowler, W. M. 1945. Polycythemia vera. *J. Iowa Med. Soc.* 35:79–82.

Troisier, J. & Le Bayon. 1937. Étude génétique des varices. *Ann. de Med.* 41:30–41.

Undritz, E. 1933. Ueber das Vorkommen einer Familie im Wallis mit "pseudodegenerativem" weissem Blutbild, bedingt durch eine Erbliche Kernform- und Kernstruktur- Varietät der Leukozyten. *Schweiz. Med. Wochens.* 63:286–288. Pl. 1.

Valentine, W. N. & Neel, J. V. 1944. Hematologic and genetic study of the transmission of thalassemia. *Arch. Int. Med.* 74:185–196. Figs. 5.

Vaquez, H. 1892. Sur une form spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante. *Compt. Rend. Soc. de Biol.* 4:384–388.

von Verschuer, O. 1934. *Erbpathologie.*

Vischer, A. 1938. Untersuchungen über Ovalocytose. *Zeits. f. Klin. Med.* 135:123–132. Figs. 3.

Vogt, E. C. & Diamond, L. K. 1930. Congenital anemias roentgenologically considered. *Am. J. Roentgenol.* 23:625–628. Figs. 5.

Waugh, T. R. 1935. Pernicious anaemia in an individual with familial haemolytic jaundice. *Fol. Haem.* 53:291–303.

Weber, F. P. 1918. Haemangiectatic hypertrophy of limbs. *Brit. J. Child. Dis.* 15:13–17.

———. 1931. A hemolytic jaundice family. *Internat. Clin.* 3.148–156.

Weber, F. Parkes & Huber, H. 1939. Stammbaum-untersuchung bei der Thrombangiitis obliterans. *Deut. Med. Wochens.* 65:256–257.

Weitz, W. 1923. Zur Ätiologie der genuinen oder vasculären Hypertension. *Zeits. f. Klin. Med.* 96:151–181.

———. 1936. Die Vererbung der Kreislaufkrankheiten. *Verh. Deut. Ges. Kreislaufforsch.* 9:11–27.

Whipple, G. H. & Bradford, W. L. 1932. Racial or familial anemia of children. *Am. J. Dis. Child.* 44:336–365. Figs. 13.

——— ———. 1936. Mediterranean disease — thalassemia (erythroblastic anemia of Cooley). *J. Pediatr.* 9:279–311. Figs. 7.

Wilkinson, J. F. & Brockbank, W. 1931. The importance of familial achlorhydria in the aetiology of pernicious anaemia. *Quart. J. Med.* 24:219–238.

Wilkinson, J. & Oliver, T. H. 1931. Some clinical conditions associated with achlorhydria. *Lancet* 220:66–71.

Williams, R. H. 1936. Felty's syndrome: report of a case with necropsy findings. *Ann. Int. Med.* 9:1247–1255.

Winsor, T. & Burch, G. E. 1944. The habitus of patients with sickle cell anemia. *Human Biol.* 16:99–114. Fig. 1.

Wintrobe, M. M., Matthews, E., Pollack, R. & Dobyns, B. M. 1940. A familial hemopoietic disorder in Italian adolescents and adults. *J. Am. Med. Assn.* 1 4:1530–1538. Figs. 10.

Wyandt, Helen, Bancroft, P. M. & Winship, T. O. 1941. Elliptic erythrocytes in man. *Arch. Int. Med.* 68:1043–1065. Figs. 4.

Yater, W. M. 1937. Thrombangiitis in Negroes. *Am. Heart J.* 13:511–533.

Zipperlen, V. R. 1932. Körperbauliche Untersuchungen an Hypertonikern. *Zeits. f. Konst-lehre* 16:93–119. Figs. 12.

Zündel, W. 1935. Ein Fall von Pelgersche familiärer Kernanomalie. *Fol. Haem.* 54:1–7.

Chapter XVI

THE BLOOD GROUPS—GENETICAL AND RACIAL ASPECTS

WHEN certain substances, mainly proteins, are injected into an animal, its tissues respond by producing an antibody. This substance is called an *antigen*. The antigen and antibody, when brought together in solution, combine specifically to form a physico-chemical union. The serum or blood-plasma of animals and man contains various natural antibodies, but others can be induced in the blood by the entrance or injection of particular substances, e.g., various bacteria or their products, or viruses. The body then reacts to produce immune antibodies in the blood, the process being one of immunization. Evidence is accumulating (see Kass, 1945) that these antibodies are produced within the lymphocytes, from γ-globulins.

When sera (blood minus the corpuscles) from different species of animals are mixed, a precipitate is formed by union between an antibody and an antigen. The amount and character of this precipitin reaction has been widely used as a measure of the near or remote relationship of the species or the groups to which they belong. Consistent results have been obtained by Nuttall (1904), who introduced the method in animals, by Mez and others in plants (see full review by Chester, 1937) and more recently by Boyden (1934, 1937) and others in animals. These methods are a valuable aid to morphology in reconstructing the phylogenetic trees of the plant and animal systems. Wolfe (1939) injected very small quantities of serum proteins from mammals, birds and reptiles into rabbits. The antisera so produced were used in determining relationships. It has recently been found that strains of certain ciliate Protozoa differ not only biochemically in the battery of enzymes they possess, but also in the antigens shown to be present by the use of rabbit serum (see Kidder *et al.*, 1945).

Other reactions of similar general character are those in which a cellular antigen unites with an antibody to produce cytolysis of the cell or haemolysis (laking) of the red corpuscles. Thomsen (1934) suggests that the same substances (agglutinins) which, by union with receptors on the red cells, produce clumping when in greater dilution, also cause haemolysis when present in greater concentration. If this is so, the difference between lysins and agglutinins is a matter of concentration only.

A type of serological reaction related to the precipitins is that in which bacterial cells or red blood corpuscles containing an antigen may react with an antibody by adhering to form clumps. This is an agglutination reaction. The agglutination of red cells is known as *hemagglutination.* When it takes place between different members of the same species it is known as *isohemagglutination.* The antigen in the red corpuscles is called an *agglutinogen,* the antibody in the serum being an *agglutinin.* These differences in human blood are the basis of what are now known as the *blood groups.* Similar serological differences have been found within many animal species.

In 1900, Landsteiner discovered that the serum of certain human beings has the capacity to cause clumping of the red corpuscles of other normal human bloods. Such bloods are said to contain *isohemagglutinogens* in the red cells and *isohemagglutinins* in their serum. These differences are of the utmost importance in connection with blood transfusion, since they cause agglutination or clumping of the red cells, with severe or fatal results, when the bloods from certain individuals are used. The nature of the clumping process itself will be discussed later. The presence and absence of particular agglutinogens are inherited as simple Mendelian units, and the frequency with which they occur varies from one human population to another. The A blood group was thus traced through several generations in a family of British Columbia Indians of mixed descent (Gates and Darby, 1934). The extensive serological, genetical and anthropological literature of the subject has been summarized in many books, of which may be mentioned Hirszfeld (1928), Snyder (1929), Steffan (1932), Lattes (1932), Boyd (1939) and Wiener (1943). The facts can be obtained from Wiener, and a list of racial blood-grouping results up to 1939 from Boyd.

Dr. Richard Lower is credited with having performed the first successful blood transfusion in 1665 (see Hollingsworth, 1928), letting out a dog's own blood and letting into its veins the blood from an artery of another dog. The first animal showed no ill effects. There is a record that Jean Baptiste Denys performed the experiment in France in 1667 of injecting eight ounces of calf's blood into a madman, who survived. Pepys in his *Diary* refers to the experiments — the replacement of a dog's own blood by that of another dog — at Gresham College in 1666; and in the following year of a "frantic" man who had "some of the blood of a sheep let into his body" without any ill effects. Lower quickly acquired fame by these experiments, which were taken up in other countries, especially France. At the instance of Robert Boyle, an account of his methods and results was published in *Phil. Trans.*, vols. i–iii, pp. 353–358.

After the early transfusion experiments of the seventeenth century, it was quickly found that they were not always successful, and in 1668 they were forbidden in France. In 1818 Blundell revived interest in the subject by experiments on dogs, followed by methods of inter-human transfusion, but progress was slow, fatalities were frequent and only about half the cases were successful. The first systematic investigation of the effects of mixing bloods was made by Landois in 1875. Finally, in 1900, Landsteiner discovered that the serum from certain individuals would agglutinate or clump the red corpuscles of certain others. The frequent previous fatalities were thus accounted for as due to incompatibility of the bloods, but this knowledge lay practically unused until the war of 1914–18 necessitated safe transfusions on a large scale.

It was soon found that there were two independent substances (agglutinogens), named by Landsteiner *A* and *B*, either of which might produce agglutination. Landsteiner at first (1901) divided human bloods into three groups. Decastello and Sturli (1902) recognized the fourth (AB) group, and Jansky (1907) and Moss (1910) made their classifications into four — now called *O*, *A*, *B*, *AB* — depending on the presence or absence of two agglutinogens. These specific bodies in the red corpuscles are acted upon by agglutinins in the serum. The blood serum contains the alternative agglutinins, called α and β (by von Dungern and Hirszfeld.

If the A agglutinogen and the α agglutinin coexisted in the same individual, his corpuscles would be clumped. Similarly B and β always occur in separate individuals. The serum (β or anti-B) of an A individual clumps the red cells of a B individual and the serum (α or anti-A) of B clumps the red cells of A. In a person of blood group A the α agglutinin is probably absorbed by the red cells as fast as it is produced, and similarly for β. In transfusion, fatal effects occur usually only when the corpuscles of the donor are clumped by the plasma of the recipient. It is recognized, however (Owen, 1928), that the plasma of the donor, if it is of high titre (strength in agglutinin), may have a serious effect in clumping the corpuscles of the recipient. This will also depend partly on the amount of blood transfused.

The tests for the A and B blood groups are made by mixing a drop of each serum with a smaller drop of the blood to be tested, on a glass slide. If there is clumping with the α or anti-A serum from a B individual, then the blood been clumped and then removed from the serum, it is found to be incapable of clumping fresh cells of the same group. The serum from an O person, containing the α and β agglutinins, can be used to clump the washed red cells from an A individual and can then be shown still to contain the agglutinin which clumps B erythrocytes.

Ashby in 1919 devised a method to determine the rate of survival of the red cells after transfusion. The normal average life of the red cells is now found to be 120 days, and if the loss is more rapid anaemia may result, but it has been found that transfused blood can survive as much as 80–120 days. If group O blood is given to an A patient, some of his blood can afterward be withdrawn at intervals and mixed with B serum. The A red cells will thus be agglutinated by the anti-B serum. The O cells will not be clumped, as they contain no agglutinogen, and so their relative numbers can be counted.

Various facts indicate that the primary effect of the A or B gene is in producing the agglutinogen which is present in or on the red cells. The presence of agglutinogens has been demonstrated in the foetus as early as the fourth month[1] of gestation (Koller, 1927) although the reactions are not so strong as after birth. In India, where group B is present in a high proportion of the population, Macfarlane (1940) found that B babies were nearer adult strength in agglutinogen than group A babies at birth. The agglutinins are generally of lower titre than in Western peoples, and she found that only 33.3 per cent of babies at a hospital in Calcutta had any agglutinin at birth. There appears to be some mechanism which usually suppresses the production of a baby's agglutinin when it would be incompatible with the red cells of the mother. Only 7 babies with agglutinins incompatible with the red cells of the mother were found among 234. This will be referred to again in connection with the Rh blood group. The average weights of full term heterospecific and homospecific infants at birth was found to be the same, and no relation was found with miscarriage, eclampsia or with digestive disorders of the infant.

The agglutinins are usually absent at birth but may become established at any time in the first two years. The agglutinins in the umbilical cord and in the child's blood at birth (Smith, 1928) are derived from the mother through the placenta and disappear within about ten days. Koller and Meier (1928) found that the serum of the baby agglutinated the blood of the mother in only about one-third of the cases where agglutination would be expected from the agglutinogens present. Of eighty heterospecific pregnancies, 12.5 per cent showed the presence in the child of an agglutinin which was not inherited and must have come in from the mother. Hyman-Parker (1942) showed that, like the AB blood groups, the agglutinogens for the M and N types were already present in the seven-months foetus while the agglutinins were established in infants seven months old. In an earlier study (Hyman, 1937) it was found that the A and B and, with one exception, the M and N agglutinogens were present in the third month of prenatal life.

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[1] They have since been detected as early as the thirty-seventh day.

Bühler (1935) finds evidence of the inheritance of the *titre* of the isoagglutinins. He believes that the titre reaches a maximum at five to ten years of age, then slowly decreasing until they vanish at ninety years. From this and other evidence, the agglutinins can be regarded as a reactive product of the tissues, secondary to the agglutinogens. Bühler examined the titre of twenty-two pairs of MZ and eighteen pairs of DZ twins. The MZ pairs were all concordant but one, while thirteen of the DZ pairs were discordant. Hence it appears that the strength of the agglutinins is genetically determined. Dahr (1941) obtained confirmatory results with 143 pairs of twins. By testing several hundred individuals, Thalhimer and Myron (1942) find that the titre of type A serum ranges from 1 : 7 to 1 : 448 and that of B serum from 1 : 28 to 1 : 3584. Thomsen (1930) first expressed the view that the A and B genes are pleiotropic in their effects, producing both the agglutinogen in the corpuscles and the agglutinin in the serum.

There is also evidence (Schäfer and Gennerich, 1939) that the thrombocytes possess group specific properties, although they are so weak that they only show an effect under special conditions in the plasma and do not cause agglutination of the platelets.

Epstein and Ottenberg (1908) first suggested that the blood groups were inherited as Mendelian units. Von Dungern and Hirszfeld (1910) tested 348 persons in 72 families and showed Mendelian inheritance of the A and B isohaemagglutinogens, each being dominant to O, the double recessive.[2] They supposed there were two independent pairs of factors, AO and BO, in different chromosome pairs. Much work was based on this view (e.g., Learmonth, 1920; Ottenberg, 1923), although certain results did not conform. The main difficulty was that in unions between O and AB parents, only children of A or B blood groups were generally found, whereas O and AB would also be expected on a two-factor theory. Such families were few, however, because the percentage of AB individuals is low in nearly all populations.

Then Bernstein (1924, 1925, 1930) from a statistical study of the group percentages as reported in various peoples, showed that the proportions of the four groups in a population are not in accord with expectation on the hypothesis of two independent pairs of factors. He concluded that A, B and O must be multiple allelomorphs, occupying the same locus in one pair of chromosomes. On this hypothesis an AB individual would have the gene A on one chromosome and B in the corresponding locus of its mate. O × AB could then give only AO or BO children. He found that in 310 families comprising 1350 individuals the multiple allele hypothesis was only contradicted by the recorded condition of 11 persons in 6 families. Bernstein's conclusion based on statistics was supported by Snyder (1926) from a study of 200 families in North Carolina. Five O × AB marriages gave 16 children in group A and 13 in group B but none in AB or O. Similarly, Thomsen (1930) recorded that from 16 marriages AB × O, 50 children were A and 60 B, but none AB or O. Boyd (1939) records from the literature a total of 483 such families with 1216 children, 598 A and 544 B. The 40 O and 34 AB children recorded can be explained through faults of technique or illegitimacy. They are nearly all from earlier papers when methods were less carefully controlled.

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[2] **Thomsen found that B is partly dominant over A, since in AB individuals the A reaction is weaker.**

In the large number of families tested by many workers a small number of O and AB children from O × AB were recorded, and Bauer (1928) proposed a two-factor theory with 11.4 per cent of crossing-over to account for them. This theory soon met with difficulties on the statistical side and it is now recognized that such exceptions are due either to errors in the technique of testing or to illegitimacy; the triple allele theory is now universally accepted.[3] Furuhata (1927, 1928) put forward a theory similar to Bernstein's but assuming separate genes for the agglutinins as well as the agglutinogens, the linkage being so close that there is no crossing-over. We have already seen that the assumption of separate genes for the agglutinins appears to be unnecessary.

We may therefore regard the theory of three multiple alleles, as established. Much evidence goes to show that dominance of A and B to O is complete. An individual homozygous for A shows no stronger clumping than one who is heterozygous (AO), and similarly for B. The AA and AO individuals can only be distinguished by the blood groups of their children. Dahr (1938) claims, however, that AA and AO can be serologically distinguished by their strength of agglutination, i.e., that dominance is incomplete after all. Similarly, Fabricius-Hansen (1939) finds in Eskimos that the N agglutination is weaker in MN than in NN persons.

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[3] Myslivec (1945) has recently raised the question of linkage again in another form. He finds the exceptions rare in matings A × A and B × B, but much more frequent when one parent is O or AB. The exceptions apparently are too many to arise as mutations, even though some are due to errors of technique or to illegitimacy. An excess of errors from such matings as A × AB or O × AB might be due to the fact that children of three or four groups can be expected, so there is little possibility of checking the result by expectation according to theory. Myslivec makes the assumption that there is a *position effect*, which is of such nature that the genes A and B neutralize each other when in the same chromosome, thus giving the blood group O test instead of AB. His statistics lead to a cross-over value about half that assumed by Bauer. He talks of combining the two theories of linkage and crossing-over, but from a genetical point of view the three genes must be either alleles or closely linked. They cannot be both. No final decision is possible on this point without further investigations.

If O was the original serological condition in man, then it would appear that A and B must have been derived from it by dominant mutations. This view, expressed by Snyder (1925), and since accepted by many workers, is not without difficulties, as will be seen later. Bernstein treated O as a separate gene and used p, q, r as the respective frequencies of A, B and O in the population; then $p + q + r = 1$, and the probabilities for the frequencies of the six genotypes will be

OO	AO	AA	BO	BB	AB
r^2	$2\,pr$	p^2	$2\,qr$	q^2	$2\,pq$

The probabilities for the four groups are then

Group	O = RR	BO + BB	AO + AA	AB
Probability	r^2	$2\,qr + q^2$	$2\,pr + p^2$	$2\,pq$

From which $O + A = (r + p)^2$, $O + B = (r + q)^2$, $r = \sqrt{O}$ and $1 = p + q + r = 1 - \sqrt{B + O} + 1 - \sqrt{A + O} + \sqrt{O}$, where, for example, B is the number of persons of B blood group. Since $p + q + r = 1$, except for chance deviation, then the difference (D) actually found, divided by its standard deviation (σ) should not exceed 2. If $\frac{D}{\sigma}$ is > 2 the result is due to errors of technique or lack of homogeneity in the population. The gene frequencies are obtained from the values $p = \sqrt{O + A} - \sqrt{O}$, $q = \sqrt{O + B} - \sqrt{O}$, $r = \sqrt{O}$.

Myslivec (1944) shows that Bernstein's deviation from $p + q + r = 1$ is not a reliable criterion of homogeneity of population. If the difference is significant the population is not homogeneous, but the converse is not necessarily true. The sum of the frequencies of O and AB is remarkably stable in the Japanese and Hungarian populations tested. There was no association between the frequency of O and A, but B and AB are both negatively correlated with the frequency of O. Myslivec found a high correlation between Bernstein's difference and the frequency of AB, and suggests that the correlation coefficient of these values could be used as a criterion of homogeneity of population.

To check the accuracy of grouping, Fisher (in Hart, 1944) suggests the test, $AB = [\sqrt{O + A} + \sqrt{O + B} - \sqrt{O}]^2 - (O + A + B)$, the excess or deficiency of AB being evaluated by means of the standard error. Fisher and Taylor (1940) suggest $\frac{A}{A + O}$ as an index for comparing European populations having little B.

The nine possible combinations of the genes are represented by $(p + q + r)^2$ and are shown below in checkerboard form with their frequencies.

♂ ♀	A p	B q	O r
A p	AA p^2	AB pq	AO pr
B q	AB pq	BB q^2	BO qr
O r	AO pr	BO qr	OO r^2

Matta (1937) made blood-grouping tests of 400 in Glasgow and 516 Egyptians in families and developed a theory based on the presence of four genes (e.g., AAAA or AAAB) for each blood group. Pauwen and Moureau (1939) show that this view is untenable.

That the blood of some A individuals clumps less strongly than that of others has long been known. Landsteiner and Witt (1926) recognized that the isoagglutinins in group A could be separated into two qualitatively different subgroups. Thomsen (1930), with Friedenreich and Worsaae (1930), divided A into two subgroups on this basis, A_1 and A_2, each of which can be combined with B. The two latter investigators tested the absorbing power of the red cells in one hundred A's and showed by their absorption curves that they fell into two classes corresponding to those of Landsteiner. Wiener and Rothberg (1933) made a study of 89 families with 440 children and found the four alleles A_1, A_2, B and O inherited in accord with expectation. More recently, evidence has been obtained of a still weaker agglutinogen, A_3 (Friedenreich, 1936), which is very rare. This is very much weaker even than A_2 and might easily pass for an O. Taylor and his colleagues found one or two probable cases in England. Friedenreich (1938) found in Denmark only six A_3 persons among five thousand. He tested seven families with three hundred persons in which it was inherited as dominant to O but recessive to A_2 and A_1. One such pedigree is given in Fig. 243. In one of these families the A_3 differed in certain points from the others in its reactions to anti-A agglutinins, indicating that it was probably a separate mutation. The A thus appears to be a relatively unstable gene, giving rise to a series of subgroups. The dominance relations are $A_1 > A_2 > A_3 > O$. In rare families, especially in negroes, a condition is found which probably represents another gene intermediate between A_1 and A_2, written A_{12}. Gammelgaard and Marcussen (1940) report a still rarer and weaker A_4.

Sachs (1943) found two sisters who were A_3 or perhaps even weaker (A_4). Another sister was A_1, the father O, the mother A_1 (evidently heterozygous for A_3). Young and Witebsky (1945) record a man who was A_3B, his sister A_2. Their father was B, the mother and her three sibs were all A_2B. This must be a mutation from A_2 to A_3, unless the paternity was misstated, which is very improbable, as the father would have to be a (very rare) A_3.

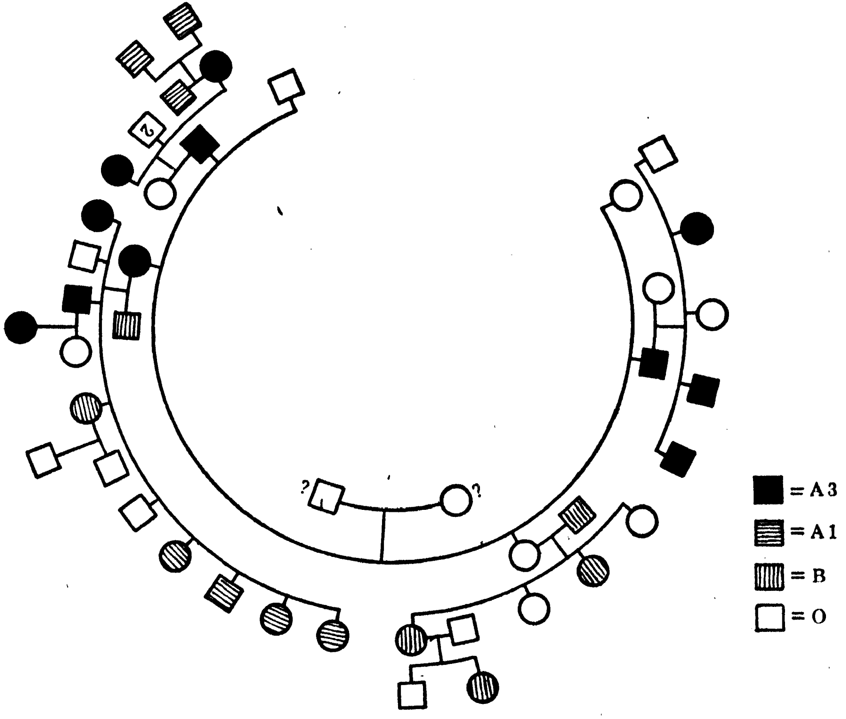

Fig. 243. Inheritance of A_3 blood group. (After Friedenreich)

Wiener and Silverman (1941) found A_3 in a colored woman and her child. In addition to the expected isoagglutinin β, an irregular isoagglutinin α_1 was present. They agree with Friedenreich that A_3 probably involves a qualitative chemical difference, and with Bernstein that all human beings produce α and β, but the incompatible isoagglutinins are absorbed as fast as formed. The very weak absorption by A_3 agglutinogen would thus account for the presence of α_1 in the serum.

Generally A_1 and A_2 blood can be used interchangeably, but in rare instances (Young, 1945) incompatibility can be acquired after repeated transfusions. In five cases patients have thus developed α_1 or α_2 agglutinins. The α_1 normally agglutinates red cells containing A_1 but not those containing A_2 agglutinogen, while α reacts with both A_1 and A_2, and α_2 with A_2.

Hirszfeld and Kostuch (1938) have suggested that B can be divided into a similar series, but there is little evidence in support of this at present, although Matta (1937) and Furuhata have distinguished B_1 and B_2, but the differences are much less pronounced. The various genetic types now known and their frequencies in a population can be grouped together as in Table 21. The rare A_3 could be combined with each of these, giving a total of eight phenotypes and fifteen genotypes.

TABLE 21

BLOOD-GROUP CLASSES

Phenotypes	*Genotypes*	*Frequencies*
O	OO	r^2
A_1	$A_1A_1 + A_1A_2 + A_1O$	$p_1^2 + 2\,p_1p_2 + 2\,p_1r$
A_2	$A_2A_2 + A_2O$	$p_2^2 + 2\,p_2r$
B	BB + BO	$q^2 + 2\,qr$
A_1B	A_1B	$2\,p_1q$
A_2B	A_2B	$2\,p_2q$

That the O blood group is merely the absence of A and B has often been doubted, seeing that O blood contains the α and β agglutinins. Hirszfeld and Kostuch (1938) regard the A and B series as two different lines of mutation from O, the presence of O-receptors in A and B blood being due to these mutations being incomplete. This O-remainder (the α and β agglutinins) would then hinder the origin of anti-O, and O would consist in a lack of the isoantibody anti-O. The different blood groups would then contain different amounts of O-substance, which develops in the order $O > A_2 > B > A_1$, the dominance relations being $A_1 \gtreqless B > A_2 > O$. Since A_1 is dominant to A_2, an individual of blood group A_1 may belong to the genotype A_1A_2. An A_1A_2 person produces only the A_1 agglutinogen.

It has long been known that if red corpuscles of one species of mammal are injected into another, e.g., horse blood into rabbit, the latter responds by forming in its serum an antibody to the red cells of the horse. Forssman in 1911 discovered that when rabbits are immunized by injections from certain organs of the guinea pig they produce antibodies against the red cells of the sheep. Intensive further work showed the widespread occurrence of this Forssman or F antigen in various species of mammals as well as various birds, fishes, invertebrates and even in plants and bacteria. It is universally present in sheep. It is present in man also, but as a component of the A antigen. A component of the B antigen (which Friedenreich, 1938, calls *G*) is similarly found in all rabbits, in guinea pigs and in the Old World but not the New World monkeys. Many more group-characters exist. These antigens are thus a species-character in one species and a group-character in another. F and G are moreover, as shown in Fig. 244, confined to certain tissues. In the diagram, circles (row II) represent the red corpuscles and triangles (row III) represent the glands of one of the species pig, sheep, rabbit, guinea pig or man. Thus F is found only in the red cells of the sheep, while in the guinea pig F is absent from the red cells and present in the glands, but G is present in the red cells and absent from the glands. The FG of the guinea pig is thus somewhat like the AB of man, but the two antigens are confined to different tissues. Various other relationships can be seen from Fig. 244. Thus the pig and the human group O have neither F nor G in red cells or glands. Row IV indicates that the red cells of some pigs are O, while in others they contain an antigen which is not the true F but another A component. Similarly, Witebsky showed that when human A red cells are injected into some rabbits they produce an anti-A serum, while others do not. The non-reactors are those which contain already an A-like substance in their organs and consequently cannot produce anti-A.

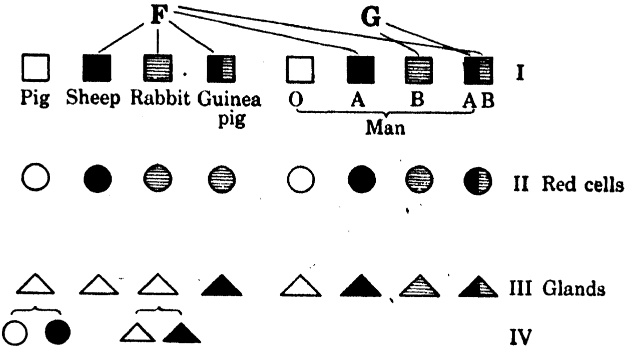

Fig. 244. Forssman antigen in various animals and man. (After Friedenreich)

It is now well recognized that an A person generally contains the A agglutinogen not only in his red cells, but that the same test can be obtained from his body fluids, e.g., saliva, tears, sweat, urine, semen, bile. It is also plentiful in such organs as pancreas, kidney, adrenals, liver and muscle, and can be found in the brain and the fat of an A individual. Furuhata states that a Japanese was convicted by "grouping" the saliva on a cigar butt which he had thrown away. The A agglutinogen is thus to be found in organs throughout the body, probably in every cell and fluid. This applies equally to the B. The agglutinins similarly occur not only in the blood plasma but also in low titre in the lymph and milk, etc.

Schiff and Sasaki (1932) found by testing the saliva that *ca.* 15 per cent of Europeans are "non-secretors" in which the reaction is confined to the red cells. The mechanism of this condition is obscure, but it is inherited as a single gene difference, the secretor condition being dominant to the non-secretor. Non-secretion applies equally to persons of the A or B group. Persons belonging to group O were tested by adding saliva to anti-O serum, but as the technique was difficult it was simply assumed that non-secretors were equally frequent among O persons. While there is no water-soluble A or B present in the saliva of non-secretors, yet these substances can be extracted by alcohol, and the group specificity of the organs can be shown by absorption experiments. Thus non-secretors contain the alcohol-soluble but not the water-soluble form of the group-specific A or B substance.

The inheritance of the secretor gene is independent of the AB blood groups and it must therefore be in another chromosome. The secretor gene is probably necessary for synthesis of the group substance by the gland cells, but apparently in no case are the human corpuscles O and the glands A or B. Brahn and Schiff found that some horses have the A substance in their saliva while others do not, but Friedenreich found that it could be present in the saliva and absent from the corpuscles of horses. Schiff (1940) found 78 per cent of secretors in the population of Berlin and 82.4 per cent in New York, but only 61 per cent among Negroes. Dahr (1941) shows that the secreting factor (saliva) is concordant in twins.

Wiener and Kosofsky (1941) made comparative quantitative tests of A_1 and A_2 saliva and A_1 and A_2 blood. They found that these differences do not correspond, indicating that the A substance in saliva differs from that in blood. The difference between the group-substances in A_1 and A_2 saliva appears to be very small compared with that which exists between the A_1 and A_2 agglutinogens in blood. A_1 and A_2 persons were shown definitely to have separate isoagglutinins α and α_1, but anti-A immune rabbit serum was found to contain only one *alpha* antibody, which reacts more intensely with A_1 than with A_2 blood. In the saliva of A_1 and A_2 persons, on the contrary, only slight differences were detected, and in one case the saliva of an A_3 could not be distinguished from that of A_1 or A_2. The group-substance in the saliva remained relatively constant, however, for each individual. The blood of persons belonging to group B was found to be equally strong in the group-substance, whether they were secretors or non-secretors, and (unlike A) the saliva of different group-B secretors was relatively constant in quantitative strength.

The A and B agglutinogens are both found to be carbohydrate-like substances. They have been isolated from human saliva and gastric juice. Schiff (1931) obtained from human sera a substance which on hydrolysis yielded a carbohydrate, and Brahn, Schiff and Weinmann (1932) isolated an A substance in very active form which on further hydrolysis showed the presence of much pentose. Witebsky and Klendshoj (1941) isolated both the A and B polysaccharides and found certain quantitative differences between them. A few milligrams of the A and B substances in 10 cc. of saline solution added to 500 cc. of O blood neutralized the isoantibodies. This blood could then be used for transfusion without any grouping. Until these substances are available in quantities, however, this method of removing the agglutinins from blood could not be used on a large scale. The A substance has been prepared, however, from peptone, pepsin and mucin.[4] Witebsky, Klendshoj and Swanson (1941) found the A and B carbohydrates similar to those isolated from Pneumococci and other micro-organisms, but the latter did not stimulate the formation of antibodies when injected into rabbits. Human B-urine is found to contain less than 1/500 as much group substance as B-saliva. In gastric juice it appears to be still more concentrated than in saliva. Boyd and Warshaver (1945) find four cases in which injection of human group B red cells into rabbits produced anti-A as well as anti-B antibodies. In two cases anti-A, some anti-O, and anti-B precipitins as well as agglutinins were demonstrated. They confirm that the A and B antigens (like the agglutinogens) are chemically rather similar, but this does not appear to be evidence against the mutational origin of the subgroups.

Witebsky and Klendshoj (1941b) found that the carbohydrate fraction from the gastric juice of a non-secretor of group B lacks any inhibitory potency to any of the three sera. On the other hand, a carbohydrate substance was isolated from the gastric juice of group O persons, which is potent in dilutions up to 1 in several hundred thousand. Absorbed normal beef serum was used, which inhibits the agglutination of the red cells of group O. There are then three carbohydrate-like substances corresponding to the A, B and O groups. This supports the view that O is not merely the absence of A and B, but that a specific substance is present. This is further supported by the fact that anti-O agglutinins are present in the sera from dogs, cats, guinea pigs, cows and fowls after they have been absorbed with AB human red cells, so that the anti-A and anti-B agglutinins are removed. Landsteiner and Harte (1940) found that the A substance from pig stomach is a polysaccharide-amino-acid complex, and others have obtained the same substance from other sources. Morgan (1943) shows that this substance combined with the conjugated protein from *Bact. shigae* forms an artificial antigen. Injected into a rabbit, it induces an extremely potent immune-body which clumps human A cells, but not B or O. This line of experimentation has been carried further by Morgan and Watkins (1944). The agglutinins are euglobulins.

We have seen that an antigenic substance which is universal in one species may be confined to certain groups in another, or the substance may be present in certain organs in one species and different organs or tissues in another; the Forssman antigen being widespread. Oliver-González and

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[4] Morgan and van Heyningen (1944) find quantities of the A, B and O substances (but no Rh) in pseudo-mucinous ovarian cysts.

Torregrosa (1944) find that the polysaccharide fractions isolated from various parasitic helminths inhibited the α and β agglutinins of human serum and the Forssman hemolysin from rabbit serum. They point out that parasites containing the Forssman antigen may account for the presence or increase in the agglutinins. The polysaccharide in these helminths is an antigenic substance common to the ABO isoagglutinins and the Forssman hemolysin. They also found a high titre of agglutinins in the serum of several malaria patients of groups O and B who had had malaria several times.

The war has led to various new methods of treating blood for transfusion purposes. Blood banks of stored blood have been collected in thousands, but this deteriorates in a few weeks. AB serum is ideal for this purpose because it contains no isoagglutinins, but only 3 to 7 per cent of donors are AB and the whole blood is of little use until the red cells have been removed. If A and B blood are mixed, the red cells of A absorb the anti-A agglutinins of the B serum and vice versa. But A is far more common in the population than B, and O is more common than either. Della Vida and Dyke (1941) point out that human plasma or serum is valuable for shock and can be stored indefinitely. For some unknown reason, when A and B sera are mixed the titre is far below that of the original components. This reaction is shown to be quantitative, depending on the titre and relative amounts of the α and β agglutinins present. They also find that a high agglutinogen content of the blood is accompanied by a high agglutinin titre. In such sera, when mixed, the absorption of the agglutinins takes place almost instantly, whereas if the agglutinogen content is low it may require several days. This wide variation makes it difficult to know in what proportions the A and B sera or plasmas should be mixed to neutralize, but generally 4 to 5 parts of A is required for 1 of B. This is partly because A_2 is weak in agglutinogen. It was found that sera could be pooled in the proportions 4 A, 1 B, 2 O or 1 AB, 4 A, 2 B, 2 O. If the blood groups are unknown, the blood of at least sixteen individuals should be pooled together, and the titre of all pools should be determined, to exclude those of high titre.

There is probably no difference between blood plasma and serum for transfusion purposes. The plasma is removed from overage stored blood and used for shock. It has an excessive potassium content and after a fortnight's storage fibrin webs are precipitated in what is then simply diluted serum. Dried plasma or serum can be stored many months, the removal of water being done either by heat or by freezing.

The exigencies of the war have led the Russians to utilize the blood of cadavers with great success for transfusion purposes. Yudin (1937) reported on a thousand cases even before the war began.

Many attempts have been made to show that the mean diameter of the red cells varies in different blood groups of the same race, as well as in different races. Friedmann and Tschkonja (1932) cite the various claims for racial differences, but after testing two hundred Russians, Armenians and Georgians they find a mean value of 7.2–7.8 μ in dry preparations, with no racial difference. Others have claimed that the Asiatic races have smaller erythrocytes, 6.8–7.3 μ, and the Northern races (Norwegians, Eskimos) larger, 8–8.5 μ. The above authors do, however, claim that in all three racial types which they investigated, the O individuals have the largest (7.15 μ) and AB persons the smallest (6.70 μ) red cells. Although the results are consistent, only fifty cells were measured in each case, so the conclusions are not reliable. Pijper (1934) used a diffraction method to measure large numbers of red cells, concluding that A was largest and B smallest. There is thus no satisfactory evidence.

One of the points of interest regarding the blood groups is that they appear to have no selective value. For most purposes, it appears to make no difference whether your blood group is O, A, B or AB. Other possibilities are not, however, entirely excluded. Graves (1934, 1935) has apparently made the only study of blood groups in relation to age of the population. He compared the blood groups of women college students, aged twenty-two to twenty-six years, with those of women sixty or more years of age. The results suggest that possibly the O blood group has a greater survival value in women than the B and AB. Tests on a larger scale according to age groups would determine whether there is such an effect, and should show whether natural selection is at work in relation to the blood groups.[5] Vorsschulte and Ziegler (1935) claim that the frequency of A is lower among scarlet fever cases than in the general population, B and AB being higher. They also find "complications" less frequent in persons of A blood group, but as only 133 scarlet fever cases were blood grouped, the result is merely an indication.

Suk (1933) examined the teeth and blood groups of 700 young men, Czech students and soldiers. Those with bad teeth showed a higher proportion of B and AB, the frequency of A being much lower than in the general population. He thinks this difference significant, but points out that in primitive peoples the condition with perfect teeth and O blood group is the most common. The linkage relations of the blood groups are considered in Chap. IV.

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[5] From blood group and age records of over 10,000 persons in northern Ireland, Hart (1944) finds no evidence that the expectation of life is lower for one blood group than another. But for some unknown reason, B male donors show a difference of two years from the age mean of donors.

As will be seen later, racial relationships have been chiefly investigated in connection with the ABO groups. In the meantime, various other serological differences in human blood have been discovered and it is probable that many more exist. Landsteiner and Levine (1928a) found the M and N blood types by injecting human blood into rabbits. Of the sera so obtained from forty-seven rabbits, four were found to contain an agglutinin for human red cells. The corresponding agglutinogen was called *M*. Some rabbit sera, when absorbed with blood of type M, were found still to clump certain specimens of human blood. This agglutinogen was called *N*. The M and N in the red cells of mankind differ from the A and B in that there are no corresponding agglutinins in the serum, so no account need be taken of them in transfusions.[6] A homozygous NN individual tests twice as strongly for N as an MN person. By testing 1190 persons, M was found in 81.7 per cent (scattered almost equally among the four blood groups), N in 76 per cent. It has been found (Taylor and Prior, 1938) that anti-M from pig serum gave the same results as rabbit serum, but these sera are difficult to make. Landsteiner and Levine (1928b) also studied the inheritance of M and N in 166 families, and Taylor and Prior tested 107 families and 218 other persons. The genotypes always correspond with the phenotypes, every person being of the phenotype M, N or MN. The corresponding genotypes are MM, NN and MN and an individual who tests only for M or N is homozygous for that factor. The M and N agglutinogens (receptors), while present in the red cells, have also been found in certain tumors. This pair of agglutinogens is inherited independently of the ABO, i.e., at a locus in another pair of chromosomes. As the MN pair are also universal in mankind, this gives another chromosome marker for linkage studies.

Thomsen and Clausen (1931) found, by testing 580 persons in Copenhagen, a frequency of MM = 30 per cent, MN = 44.6 per cent, NN = 25.5 per cent. Hyman (1935) prepared M and N sera by injecting into rabbits washed human red cells of known donors, thus obtaining sera which contained agglutinins against the agglutinogens M and N which corresponded in every way with those of Landsteiner and Levine. She tested 578 persons, including 100 families, for the heredity of A, B, M and N, finding no exception to the rule that they represent two independent pairs of genes. She also examined 20 pairs of MZ and 2 pairs of DZ twins for A, B, M and N, finding the MZ always in agreement.

The following summary of results, from Wellisch (1938), shows (Table 22) the independence of the ABO and MN, based on tests of 26,358 individuals.

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[6] Among many thousands of human sera examined, four have, however, been found to contain an anti-M agglutinin (Wiener and Forer, 1941).

TABLE 22

INDEPENDENCE OF ABO AND MN BLOOD TYPES

	% *M*	*MN*	*N*
In group O	32.5	46.5	21.0
In group A	32.6	48.0	19.4
In group B	31.8	47.7	20.5
In group AB	30.6	50.5	18.9

Boyd (1939a) showed that in 5281 parents and children tested for M and N there were only 11 discrepancies from the theory of Landsteiner and Levine. Since the MN tests will detect about one-sixth of illegitimacies, this leads to the conclusion that about 12 children per 1000 were illegitimate, which corresponds exactly with the estimate from the ABO groups.

Friedenreich (1935) has since found a rare weak factor, N_2, which is recessive to N_1 but is not obscured by the presence of M. Fourteen members had N_2 in three generations of one family. Pietrusky (1940) found N_2 in five families and traced its inheritance in three. It is found (Bruynoghe, 1936) that the M and N agglutinogens can be detected in the saliva of M or N persons, but unlike A and B, it is not constantly present in the individual. M and N may also be absent from the saliva of an A or B secretor, or on the contrary a non-secretor for AB may show MN in the saliva. Recently Boorman and Dodd (1943) have shown the presence of the M and N substances in the tissues and body fluids but they are relatively insoluble in water. Kosjakov and Tribulev (1939) found that they were not destroyed by boiling or by cold. Results collected by Alley and Boyd (1943) show that the Chinese have *ca.* 15 per cent of N, the Japanese *ca.* 18 per cent, Amerindians only 4 to 9 per cent, Ainu *ca.* 32 per cent. N is also much higher than M in the Australian aborigines. Bodies resembling M have been demonstrated in the orang, gibbon and in rhesus monkeys, while both M and N have been found in the chimpanzee (Strandskov, 1944). Another agglutinable factor, P, was obtained (Landsteiner and Levine, 1928a) by injecting the blood of colored persons into rabbits. Thus the A, B, O, M, N and P genes in their various combinations give thirty-six varieties of human blood, but the P has been as yet but little used.

Landsteiner and Levine (1931), in a further study of P, found only four families (with eighteen children) among seventy-one families tested, which were entirely negative to P. They found evidence that P represents a group of factors determined by rabbit serum. Rabbits in which the anti-P agglutinin could be demonstrated were mated together and the incidence of the agglutinin was higher in the offspring. P is dominant to its absence, so the genotypes are **PP**, **Pp** and **pp**. Dahr (1939) obtained P-serum from Landsteiner and tested fifteen families with seventy children, finding the P inherited from parent to children. He also tested thirty-three pairs of MZ twins, using a pig serum, and found them all concordant. Dahr, Offe and Weber (1940) tested 210 families with 748 children in Cologne, finding only 3 exceptions, ascribed to illegitimacy. They found P independent of both ABO and MN in inheritance, the frequency of P in the Cologne population being 76.5 per cent (2441 tested), whereas in Negroes it appears to be 97.8 per cent (Landsteiner) and in New York whites 81.9 per cent. P has been little used because of the difficulty in obtaining strong sera (see Wiener, 1943).

Landsteiner, Strutton and Chase (1934) found that two rabbits, when injected with Negro blood having P, produced another (Hunter) immune serum. The corresponding agglutination factor was found to be present in 14 out of 191 colored persons tested, but in only 2 out of 387 whites, indicating its much higher frequency in the Negro race.

Other serological factors described (see Wellisch, 1938) include Q of Furuhata (**QQ, Qq, qq**), which is closely similar to P and may prove to be the same. It was found in 31 per cent of Japanese, while P is stated to be present in 61.6 per cent. Ee of Sugischita, demonstrated with eel serum, occurs in A, B and AB but not in O blood. H of Schiff also requires further study. Dahr (1941) has since tested P in 300 pairs of twins, including 123 MZ pairs, in all of which it was concordantly present or absent, and 177 DZ pairs, in some of whom it was discordant. He also finds a probable difference in the strength of P in different families.

In a series of papers, Taylor and his colleagues have studied the distribution and inheritance of the $\mathbf{A_1}$, $\mathbf{A_2}$, **B, O, M** and **N** genes in the English population, confirming the Bernstein theory of inheritance of the ABO, as shown by application of the χ^2 test to the statistical results. The main results, in comparison with others, are given in Tables 24 to 26 (pp. 711–713). Taylor and Prior (1939b) list the results of fifty-five investigations of the M and N types in various races. The χ^2 test indicates that in seven of them there was faulty technique. In a population with M and N in equilibrium, 25 per cent M : 50 per cent MN : 25 per cent N would be expected only when *m* and *n* each equal .5. From all the pooled data from tests of 77,206 persons they found 30.9 per cent M : 49.4 per cent MN : 19.7 per cent N. An O condition in which M and N are both absent never occurs, so the lower frequency of N cannot be accounted for through lack of penetrance. A few of the percentages for different races are given in Table 26, p. 713. Taylor and Prior devised a mathematical test for homogeneity of population as regards the M and N and found that the total results were not homogeneous;[7] there was also some evidence of heterogeneity within Russia, the British Isles and south Germany, with greater diversity between different countries. The differences are, however, generally small (as may be seen from Table 25), and somewhat ambiguous. M is greater than N in nearly every case except the Ainu and the Paiwan aborigines of Formosa and certain others (see below). The Taiyal and Paiwan of Formosa both show a large excess of MN over 50 per cent. This is perhaps due to lack of care in typing. In the Pueblo and Blackfoot Indians there is a large excess of M over N, but the numbers tested were small. N is, however, low in American Indians and still lower in Eskimos, while it is high in Ainu, Batavians, Javanese and Sudanese and extremely high (67.4 per cent) in Australian aborigines.

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[7] Wiener (1943) points out that in MN × MN matings the excess of MN children observed probably results from less care in typing; since children of all types can occur, there is no check on the accuracy of the tests. Similarly with A × B.

Stevens (1938) developed methods for determining the gene frequencies from known frequencies of the phenotypes MN, ABO and A_1A_2BO and for testing the heterogeneity in different populations. It will be seen that the Hawaiians and the Blackfoot-Blood Indians are very much alike, both having 60 to 80 per cent A and the A's practically all A_1. The Australian aborigines have 60 per cent A, like the Hawaiians, and they too have only A_1 (see Table 24, p. 712). About 20 per cent of the A in Europeans is A_2 and it appears that this is a secondary mutation from the original stronger A_1. A_2 seems to be highest (67 per cent) in Negroes. Levine and Wong (1943) find only 3 per cent in 150 Chinese. Waller and Levine (1944) find in Japanese, 50 A_1 : 10 A_2.

Values for $\frac{A_2}{A_1}$ in other races are given in Boyd (1939a). The relatively high frequency of A_2 in North Wales, Ireland, Basques and Negroes, and its very low frequency or absence in Indians, Eskimos and Hawaiians, strongly suggests that various races have different mutation rates for A_2.

Dahr and Bussmann (1938) studied the inheritance of A_1 and A_2 in 106 families with 450 children in Cologne. Two exceptions to expectation were found. In one the father was A_1BN, the mother A_2M. Five children were all A_1MN but the last child was A_1BMN. These results were confirmed by various repeated serological tests. Since B and N were from the father, illegitimacy may be excluded, and possible exchange of babies was excluded as birth took place at home in the country. The only explanation is that the A_2 of the mother changed to the stronger A_1. If the child had not happened to have B like the father, the occurrence of this submutation could not have been detected. In the other case the father was OMN, the mother A_2M, the children A_2MN, OMN, A_1MN, A_2M, OMN, A_2M. The third child represents again an apparent change of A_2 to A_1, although in this case illegitimacy is not excluded. Dahr thinks the strength of the clumping indicates that the child is AA, not AO, and suggests illegitimacy as a possible explanation. Some twenty other similar cases in the relatively small number of A_1–A_2 tests made in families, can be explained on the same basis. Dahr (1941) tested 133 pairs of MZ and 197 pairs of DZ twins, finding the former all concordant as regards A_1, A_2, B, O, M and N.

The genetics of the blood groups is comparable with that of the various forms of color-blindness. In the latter it is clear that the subgroups or quantitative differences are relatively labile genes which can mutate in either direction with relative facility, whereas the main genes are more stable and no mutation from one to the other is known (see p. 142). In the same way it may be expected that while mutations between A_1 and A_2 may occur, those between A or B and O will be much more rare.

Rh

A new blood group, recently discovered (Landsteiner and Wiener, 1940), is of special interest in several respects. An immune serum was obtained by injecting the blood of rhesus monkeys repeatedly into rabbits or guinea pigs. This serum reacted with human blood, producing agglutination of the red cells independently of AB, MN or P. This new factor was (1941) designated *Rh*. It was present in about 85 per cent of 448 whites tested, while 15 per cent were Rh−. It corresponds to the agglutinin described by Levine and Stetson (1939) in a woman. In a larger series of 1035, tested by Levine, Vogel, Katzin and Burnham (1941), about 14 per cent were Rh−. Unlike the MN, the Rh agglutinogen can induce the formation of isoantibodies (agglutinins) in certain individuals, so it has to be taken into account in transfusions. It is apparently inherited independently of the AB, MN or P agglutinogens, and should serve as a marker for a fourth pair of chromosomes. Only 9 out of 113 Negroes when tested were Rh−, so it is probably absent in about 8 per cent of that race. In American Indians, Landsteiner, Wiener and Matson (1942) found only one Rh-negative among 120 full-blooded Indians belonging to tribes in Washington State and adjacent areas, with an intermediate frequency in 155 of ancestry mixed with whites. This suggests that practically all Indians of pure blood have the Rh gene. Levine and Wong (1943) tested 150 Chinese in New York and found only one Rh−. This, we shall see, accounts for the known rarity of erythroblastosis in Chinese.

The inheritance of Rh was tested in 60 white families with 237 children, **Rh** being dominant to its absence (**rh**). There are then three genotypes, **RhRh, Rhrh** and **rhrh.** Gene and genotype frequencies have also been calculated.

It has further been shown (Levine and Katzin, 1941) that the Rh agglutinogen is not present in the saliva or seminal fluid and is probably confined to the red cells.

More recently, Witebsky and Mohn (1945) found that there are secretors and non-secretors for the Rh as for the AB. About 80 per cent of persons are secretors, and secretion of the Rh substance into the amniotic fluid is independent of the secretion of the AB agglutinogens. The decidua contain the agglutinogens of the mother, the amniotic fluid that of the baby.

In rare cases, transfusion of blood of the same group as the patient, or of O blood, has led to violent and sometimes fatal hemolytic reactions. Wiener (1941) described ten such cases and found that in seven of them the Rh was involved. If, for instance, the donor and recipient are both O, but the donor is Rh+ while the recipient is Rh−, then hemolysis will result.

The greatest importance of the Rh is in connection with pregnancy. There is definite evidence that the human placenta is permeable to various antibodies (Wiener and Silverman, 1940). Hirszfeld (1928) at an early date developed the conception of heterospecific pregnancy based on the A and B blood groups. He suggested that if A or B is present in the foetus but not in the mother, the maternal agglutinin could act on the foetal blood to produce icterus gravis. This theory was abandoned for lack of evidence, but has now been revived in relation to the Rh.[8] It has also recently been shown that malaria can be transmitted through the placenta to the foetus.

Macklin (1937), from a study of fourteen reported families in which icterus gravis neonatorum or foetal hydrops (hydramnios) occurred, differing in degree rather than in kind, showed that frequent abortions, stillbirths and macerated foetuses occurred to mothers who had one or more infants with erythroblastosis foetalis. She suggested that the condition was inherited as a dominant mutation. Darrow (1938) reviewed the various theories and agreed that the familial occurrence indicated some form of hereditary transmission, although it could not be of the type suggested.

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[8] In two recent cases of erythroblastosis foetalis (Polayes, 1945) the mother and child were both Rh+, but the mother was O and the baby A. In McCall's (1945) case an Rh incomplete antibody was found in the mother. Levine and Gilmore (1945) bring further evidence that blocking or incomplete antibodies represent a condition in which the Rh+ red cells are specifically coated with the antibody so they cannot react to the agglutinins in anti-Rh sera. In further experiments, Coombs and Race (1945) find that the incomplete antibody to antigen D in Fisher's notation is a protein of low molecular weight and remarkably thermostable. Further experiments show that the surface charge on the red cells is not alone responsible for agglutination.

As early as 1884 Ashby reported a family of five children, the last three of which died of jaundice soon after birth. The subject was reviewed by Diamond *et al.* (1932) and by Hawksley and Lightwood (1934). The latter reported a family in which three stillbirths were followed by three icteric infants who died in a few days. McFeeters (1939) cited a family in which three different mothers each had an anencephalic foetus with hydramnios (dropsy of the amnion). The respective fathers were related as father and two sons, so the condition appeared to be inherited through the father but is probably explained by the fact that they were Rh+ and their wives Rh−. From a study of 25 women having repeated abortions and miscarriages, however, Hunt (1945) concludes that the Rh is not an important factor in their production. He finds the average incidence of abortion in women 19.3 per cent, but others give higher figures.

Transfusion accidents proved to be rather frequent in connection with pregnancy when the known blood groups indicated no source of error. The serum of these women was shown by Levine, Katzin and Burnham (1940) to contain atypical agglutinins similar to anti-Rh, having greater activity at 37° C. than at lower temperature. In these cases the mother showed a high incidence of toxemia, spontaneous abortions and miscarriages, stillbirths and macerated foetuses. These are all believed to result from the isoimmunization of the mother by the blood of the foetus. Levine *et al.* (1941) made blood tests of 153 mothers who had delivered infants with one of the three clinical forms of erythroblastosis foetalis, i.e., foetal hydrops (hydramnion), icterus gravis or anaemia of the newborn. There had frequently been previous miscarriages or stillbirths. Schwartz and Levine (1943) find the frequency of erythroblastosis about one in 200 deliveries.

In 93 per cent of these cases, erythroblastosis was shown to result when the mother was rh, the father and the child Rh. The Rh agglutinogen of the foetus then passes through the placenta and develops the corresponding agglutinin in the mother's blood (isoimmunization). This agglutinin from the mother's circulation then hemolyzes more or less severely the blood of the foetus. It is estimated that erythroblastosis foetalis in some form occurs once in 438 pregnancies. The Rh agglutinin is shown to be present in the mother's blood. In about 10 per cent of cases the mother was Rh positive and some other antigenic factor must then be involved. Murray (1944) tested two hundred antenatal mothers and found 12.5 per cent of them to be Rh−, at least two having already an Rh antibody.

The "inheritance" of erythroblastosis foetalis then depends on the Rh factor. The mother must be **rh** and the father **Rh.** If the father is homozygous (**RhRh**), then the first child or two may be born normal before the mother is immunized, but all subsequent births will be likely to show any condition from anaemia or icterus gravis to early abortion. If the father is heterozygous (**Rhrh**) and the births are sufficiently spaced for the mother to lose her isoagglutinins in the interval, then half the children may be expected to be normal. It has recently been found, however, that in some cases the mother may retain Rh sensitivity throughout life. An inherited isohaemagglutinogen is thus shown to be the cause of many cases of anaemic, lethal and stillborn infants, and probably also of some cases of repeated abortion and miscarriage. Witebsky, Anderson and Heide (1942) have shown in a case of erythroblastosis foetalis that the mother's milk actually contained an Rh antibody. These results have been confirmed by Langley and Stratton (1944). Levine (1945a) points out that transfusion of Rh+ blood into a female child or infant who is Rh− will produce permanent antibodies in her blood, so that her first child by an Rh+ father will be erythroblastotic because the mother is already immunized.

In some 13 per cent of all random matings the father is **Rh** and the mother **rh,** but only a small percentage of such marriages develop erythroblastosis foetalis or similar conditions. This is apparently because in most cases the placenta is not permeable to these bodies in the sera of the mother and child. Since the same mother can produce these conditions repeatedly it is supposed that a *permeable placenta* is determined constitutionally by the mother. When the father is heterozygous and there are twins, one of whom is Rh+ and the other Rh−, only the former will be affected. It appears that a preponderance of the fathers are homozygous (**RhRh**), the marriages of **RhRh** men with **rhrh** women being *ca.* 5.7 per cent. Stern and Charles (1945) show that, disregarding a possible factor influencing placental permeability, cousin marriages in which the woman is **rhrh** should produce only seven-eighths the frequency of erythroblastosis found in non-cousin marriages of **rhrh** women.

Cooley (1941) found 15 cases of erythroblastosis foetalis in 22,209 cases at St. Louis Maternity Hospital. In a total of 153 cases, 93 per cent were due to the above explained causes.

Levine suggests that in the case of the A and B blood groups no such reaction occurs because these agglutinogens are generally present in all the tissues. In non-secretors, however, the relation is the same as with the Rh, which is confined to the red cells, and foetal effects may thus be expected when A or B is present in the foetus and not in the mother. Such so-called incompatible matings occur in 35 per cent of all random unions, but in a group of 150 cases with foetal deaths the incidence of incompatible matings was as high as 54 per cent (Levine, 1942). Furthermore, Hirszfeld (1928) found that in matings A♂ × O♀ the incidence of A offspring is less than in O♂ × A♀, presumably because of selective foetal death. A form of selection may then be taking place in any population, depending on its ABO composition.

Boorman, Dodd and Mollison (1942) have made a report, confirming this work and recording further cases. They point out that, whether the immunizing factor be Rh, A or B in the red cells, it is necessary to postulate the actual entry of foetal erythrocytes into the maternal circulation to produce immunization. In such cases the placenta, contrary to generally accepted views, must be not merely permeable but sufficiently porous for red cells to pass at certain points. The above authors cite forty-eight cases of erythroblastosis, in forty-four of which anti-Rh agglutinin was present in the mother, although in some cases immune anti-A or anti-B agglutinins were also found. In four cases only the anti-A and anti-B were observed, confirming that these can produce erythroblastosis. Malone (1945) cites a case in which the mother, a primipara, was of blood group ORh+, the father ARh+. The twins both died of erythroblastosis, but the father's cells were agglutinated by the mother's serum only to a titre of 1 in 32.

Taylor, Race and Prior (1942) find that a titration method is frequently necessary to determine the presence of Rh antibodies, as the reaction may only occur with diluted serum. Three further papers on this subject are to be found in *Brit. Med. J.* for Sept. 4, 1943. Boorman and Dodd (1943) show that the Rh substance is widely distributed in the tissues but is almost entirely absent from the body fluids, apparently because it is almost insoluble in water. They suggest that possibly the absorption of agglutinins crossing the placenta from the maternal to the foetal circulation is affected by the soluble group specific substances contained in the body fluids.

Wiener (1942) points out that affected infants are all **Rhrh,** so that equal numbers of **Rh** and **rh** genes are lost. He computes the result over many generations. If **Rh** and **rh** began equal they would not change, but if they began unequal then the less frequent gene might be eliminated in some thousands of generations. This is regarded as evidence against the mutation theory of their origin. There is, however, no cogent evidence that the **rh** gene is being eliminated by selection. Such selective action would prevent an Rh+ population, even with a very high mutation rate, from attaining as much as 15 per cent Rh−. But if some past populations were nearly 100 per cent Rh−, then from crosses with Rh+ tribes, like the American Indians, a hybrid population could result, like that of New York, with 15 per cent Rh−. This leaves us without an explanation of how some races came to be Rh+ and others Rh−. Haldane (1942) reached similar conclusions. Taking the frequencies for American whites as 36.9 per cent **RhRh,** 47.7 per cent **Rhrh,** and 15.4 per cent **rhrh,** he deduces that 9.36 per cent of all conceptions are of **Rhrh** babies by **rhrh** mothers. With selection against **rh** gametes, they will increase if their frequency, p, is more than $\frac{1}{2}$, and decrease if p is less than $\frac{1}{2}$. If the placental permeability is controlled by a gene, it must obviously be much rarer than the **rhrh** condition.

Levine (1942) found three main varieties of anti-Rh serum giving, in whites, 87 per cent, 85 per cent and 73 per cent respectively of reactions. He calls them *anti-Rh*$_{1.2}$, *anti-Rh*$_1$ and *anti-Rh*$_2$, the middle one being considered the standard. With anti-Rh$_2$ he obtained the following results:

Whites	334	73% Rh+
Colored	118	46% Rh+
American Indians	69	58% Rh+
Chinese[9]	150	93% Rh+

Hence both Negroes and Indians are low in Rh$_2$.

Wiener and Sonn (1943) have tested 40 families with 138 children for Rh and support the view that it is a simple dominant, independent of the ABO groups and the MN types. It is thus a marker for a fourth chromosome.

Wiener and Landsteiner (1943), from further studies, divide the **Rh** factor into three main alleles, which they call **Rh**$_1$ > **Rh**$_2$ > **rh,** with dominance relations as indicated, the relative frequencies being **Rh**$_1$ about 48 per cent, **Rh**$_2$ 16 per cent, **rh** 36 per cent in the population.

[9] Wiener, Sonn, and Yi (1944c) find in 138 Southern Chinese in New York, 1.5–5.1 per cent Rh− according to the serum used. Waller and Levine (1944) tested 150 Japanese in New York and similarly found only 2 to 38.6 per cent Rh−. Pinkerton (1944) tested 611 orientals (Chinese, Filipinos, Hawaiians, Koreans and Japanese) in Hawaii, finding only one Rh−. By contrast, of 499 Caucasians, 13.6 per cent were Rh−, but only 1.8 per cent of 164 Caucasians × Hawaiians were Rh−. Simmons, Graydon and Ouwehand (1945) tested 296 Indonesians from the East Indies and found all Rh+ except two from Celebes who might have had a white ancestor in the 17th century. By contrast, Simmons, Graydon, Jakobowicz and Bryce (1943) found 17.66 per cent Rh− among 3641 white Australian blood donors. They found possible linkage with the ABO. Simmons, Graydon and Hamilton (1944) tested 281 aborigines from different parts of Australia and found them all Rh+. Wiener, Unger and Sonn (1945), in a further study of the distribution of the eight Rh types in New York whites, find striking differences from the Negroes. Khanolkar and Sanghvi (1945) tested 70 Hindus in Bombay, finding them all Rh+, while one of fourteen Parsees and one among eleven Indian Christians were Rh−. Combined results (Wiener, 1939) for 4092 Chinese gave 0.7 per cent Rh−, for 1379 American Indians 0.8 per cent, for 500 Negroes 5.5 per cent. Lubinski, Benjamin and Strean (1945) tested 967 Jewish mothers and infants in Montreal, finding 8.4 per cent Rh−.

Wiener (1943a) and Race *et al.* (1943) announced further variants of the **Rh,** and it was evident that the full analysis of these subgroups had not yet been reached.

Levine (1944) concludes that at least 90 per cent of cases of erythroblastosis foetalis can be attributed to Rh_1, Rh_2 and Rh′, but it can also be produced by A, B, or Hr. He points out that the total area of the foetal villi is 70 sq. ft. and that there are microscopic breaks in the chorionic villi, probably allowing a minute quantity of foetal blood to enter the maternal circulation. Macklin (1944) suggests that Rh incompatibility would be a better term than erythroblastosis, because the two conditions are not coextensive. The Prussian blue test for iron in the liver shows that hemolysis can occur in foetuses which are lost early in gestation.

For some unknown reason, $\mathbf{Rh_2}$ does not usually produce erythrosis. The mothers of erythroblastotic infants are **rh** or **Rh′**. However, Waller, Levine and Garrow (1944) record the case of a mother who was $\mathbf{Rh_2}$; she produced an erythroblastotic infant which was **Rh′** like the father.

Race, Taylor, Cappell and McFarlane (1944) now recognize seven Rh alleles, which may be designated $\mathbf{Rh_0}$, $\mathbf{Rh_1}$, $\mathbf{Rh_2}$, **Rh′**, **Rh″**, **rh** and $\mathbf{Rh_y}$. Wiener (1944) recognizes six, regarding $\mathbf{Rh_y}$ as related to the others in the same way that O is related to AB. Wiener, Sonn and Belkin (1944b) conclude that Rh antibodies and agglutinogens both play a role in the Rh reactions. But they find that only about 2 per cent of Rh− persons respond to transfusions of Rh+ blood by producing antibodies, unlike the A and B which always produce antibodies. They suggest that this may be because the Rh is a subsurface antigen while the A and B agglutinogens are at the surface of the red cells; or there may be fewer Rh than A or B hapten groups in the red cells. There is need for further study of the nature of these reactions. It appears to the present writer that the whole serological theory of clumping requires an overhaul. Marrack (1938) discusses at length the nature of antigen-antibody reactions. In the recent new edition of Landsteiner's book (1945) the subject is fully considered, and by Boyd (1943). See also Boyd and Hooker (1938). Rouleaux formation occurs in sera from pregnant or puerperal women. This seems to have a bearing on the nature of agglutination. From a quantitative study of the precipitin reaction of the type III Pneumococcus polysaccharide with horse serum, Heidelberger and Kendal (1935) find that a bimolecular chemical reaction is involved, followed by a series of competing bimolecular reactions which result in precipitation. Heidelberger (1938) concludes not only that antibodies are proteins but that almost any change at any part of the molecule will produce a characteristic change in specificity. There is thus increasing evidence that serological reactions are fundamentally strictly chemical in nature.)

In a study of reactions between antigen and antibody, using Langmuir's film method, Rothen (1945) finds that the reaction can take place through as many as four double layers of stearic acid, although they act as a perfect screen for certain types of reaction, e.g., the adsorption of a layer of insulin molecules by a layer of protamine. This seems to show that specific interaction between antigen and antibody can take place without contact, at a distance measured in hundreds of Ångstroms. This would help to explain why so many antigens can be present in or near the surface of the red corpuscle without interfering with each other.

Wiener and Karowe (1944) have devised a representation of the haptens in the ABO blood groups which visualizes their ideas of the antigen-antibody reactions. While this may help toward an understanding of the various relations between the agglutinogens and agglutinins, the assumption that in **AA** (homozygous) individuals the polar groups on the erythrocytes are duplicated at each end of the hapten is not in harmony with genetic knowledge. Such differences between homozygotes and heterozygotes are unknown and highly improbable.

Study of the properties of various mixtures of anti-Rh sera leads to complicated relations between the various agglutinogens and agglutinins (Race, 1944; Stratton, 1944). Standard anti-Rh serum agglutinates the red cells of the genotypes **Rh**$_1$ and **Rh**$_2$, while anti-Rh$_1$ serum agglutinates the former cells but not the latter. Race observed that if red cells of the genotypes **Rh**$_2$**Rh**$_2$ or **Rh**$_2$**rh** are added to a mixture of these two sera, agglutination due to the standard anti-Rh serum does not occur. Also if Rh$_2$ cells are suspended for a few minutes in anti-Rh$_1$ serum, not only is there no agglutination but these Rh$_2$ cells, after being washed, can no longer be agglutinated by standard anti-Rh serum.

On the basis of such relationships between the Rh factors, Fisher drew up a formulation of antigens, genes or alleles, and antibodies in which the three forms of allelomorphic antigens are denoted by Cc, Dd, Ee, the antibodies with which they react being denoted by the corresponding Greek letters. Each gene appears to be associated with a selection of three antigens from these three pairs. This system accounts for the seven alleles and predicts an eighth (**R**$_z$) corresponding to CDE.[10] **Rh**$_1$ is CDe, **Rh**$_2$ cDE, **Rh**$_0$ cDe, etc. This system also suggests the existence of two more antibodies reacting with d and e respectively, making a total of six. Each gene is thus associated with three allelic antigens or, as an alternative, three closely linked loci are involved. This new complication in the genetics of the Rh alleles awaits further development. In harmony with such relations, Dockeray and Sachs (1944) find two cases in which marked amounts of anti-Rh were present in the mother's serum but the child was normal.

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[10] **Rh**$_z$ has recently been demonstrated (see Murray, 1944) and the Hr of Levine is apparently the same as St of Race and Taylor. Race *et al.* (1944) have analyzed the **Rh** alleles in fifty-six more families. They and Snyder (1945) both suggest the use of R instead of Rh, since the other blood groups are represented by single letters.

Wiener (1944a) subsequently, from a study of **Rh** genes with intermediate reactions, introduces a scheme of eight **Rh** alleles, but the analysis of this nest of genes is evidently not yet final. Murray (1944a) suggests a numerical nomenclature of the subgroups. Murray, Race and Taylor (1945) find a family with $\mathbf{R}_z$ and alter certain antigenic formulae of Fisher. The relations of the four systems are compared in Table 23.

TABLE 23

SYSTEMS OF SYMBOLS FOR THE Rh ALLELES

Wiener	*Fisher*	*Murray*	*Snyder*
Rh_z	CDE	Rh 123	——
Rh_1	CDe	Rh 135	R^0
Rh_y	CdE	Rh 126	$R^{0'('')}$?
Rh′	Cde	Rh 156	R′
Rh_2	cDE	Rh 234	$R^{0''}$
Rh_0	cDe	Rh 345	R_0
Rh″	cdE	Rh 246	R″
rh	cde	Rh 456	r

A new antibody (Br), which is identical with Fisher's predicted η, has now been found (Mourant, 1945). It also turns out that Hr and St are not the same antibody (Race, McFarlane and Cappell, 1945), but other evidence supports the hypothesis of Fisher although the very rare Rh_y has not yet been found. Since this was written, Levine (1945b) points out that Hr and St are really the same, the supposed difference being based on an error. They contain identical antibodies corresponding to Fisher's γ. The point has now been reached where an international committee is necessary to settle the future nomenclature of all the Rh alleles.

In a study of Negroes in New York City, Wiener, Belkin and Sonn (1944) confirm that O and B are higher and non-secretors more frequent than in whites. The A_2 is also a higher proportion of A. Intermediates between A_1 and A_2 were found and designated A_{12}. There was no difference from whites in the MN, but $\mathbf{Rh}_0$ was 25 to 42 per cent in Negroes and only 2 to 3 per cent in whites, so that the $\mathbf{Rh}_0$ frequency might be used as an index of Negro purity. $\mathbf{Rh}_1$ was twice as frequent in whites as in Negroes.

Wiener, Davidsohn, and Potter (1945) tested the **Hr** factor in 239 whites and 49 negroes in New York. They agree with Race and Taylor that anti-**Hr** reacts with $\mathbf{Rh}_2$, **Rh″**, and **rh,** but not with $\mathbf{Rh}_1$ and **Rh′**. Among whites, 25 per cent were negative for **Hr** and **P,** but only 2 per cent of negroes were negative for both. **Hr** and **P** are, however, independent. **Hr** appears to be most frequently involved when the mother is **Rh+** and the child shows hemolysis.

Another Rh allele has since been found, and Levine (1945) concludes that Hr belongs to the Rh allelic system of genes. There are thus six Rh antigens, each with a specific antiserum. These antigens are inherited by means of eight Mendelian genes, giving 36 different genotypes, 27 of which can be distinguished serologically.

McCall and Holdsworth (1945) report two families in which St produced hemolytic disease of the newborn. Although isoimmunization with this factor should be as frequent as with Rh, it is much less so, probably because the St antigens are usually weak. Baar (1945) points out that anti-Rh agglutinins are seldom found in the sera of hemolytic babies and shows how the blocking test can be used to detect isoimmunization in Rh− women. He thinks it premature to accept fully Fisher's scheme of Rh genes, because a mosaic of serological reactions need not always have a corresponding series of chemical structures in the antigen.

Callender, Race, and Paykoc (1945) find three new antibodies in a woman suffering from lupus erythematosus diffusus, this disease being regarded as the result of some antigen-antibody reactions. One of the new antigens belongs in the Rh series and is designated C^w (at Fisher's C locus). Another, known as the Lutheran antigen, is independent of ABO, MN, P and Rh. It is dominant in heredity and has an estimated frequency of 8–9 per cent in the English population. The third (Levay) antigen is rare but was found in father and son. Many more probably await discovery.

The families now tested for inheritance of Rh genes (Wiener and Sonn, 1945) number 197 with 463 children. The only two exceptions were known to be illegitimate. Wiener assumes Rh_0, Rh′ and Rh″ as three dominant alleles with five corresponding agglutinogens, Rh_0, Rh′, Rh_1, Rh″ and Rh_2, where Rh_1 contains Rh_0 and Rh′ together and Rh_2 contains Rh_0 and Rh″. The ABO, MN, P and Rh belong in four different chromosomes and give 288 different varieties of blood.

Boorman, Dodd and Mollison (1945) studied the development of immune antibodies to A, B and Rh, (a) after transfusion, (b) in pregnancy. Anti-Rh was usually produced only after repeated transfusions or pregnancies. Boyd (1945) recently reviewed the various Rh factors and their relations.

In a recent further study, Wiener (1945) accepts Fisher's hypothesis and postulates three varieties of Hr-antisera, Hr_0, Hr′ and Hr″ corresponding to the Rh_0, Rh′ and Rh″. He also discusses other recent developments.

Serology and Race

The simple unitary nature of the blood groups, their inheritance as Mendelian units and the fact that they appear to have no selective value as between adults gives them great advantages over other characters in the study of racial relationships. Nearly all other racial differences, for example in head shape, eye color, hair characters and stature, are not only quantitative but depend upon multiple factors which are genetically much more difficult to analyze. The blood groups are, moreover, unaffected by environment, whereas all the measurements taken by physical anthropologists are more or less subject to influence by external conditions, and the degree of that influence is difficult to measure. The blood groups are therefore a series of additional anthropological characters which should be of great value in tracing racial histories. They should also prove to be of great importance in connection with linkage studies, although, up to the present, evidence of their genetic linkage has been mainly negative. Different blood groups may ultimately serve as markers for many of the chromosomes.

The Hirszfelds (1919) made the first records of racial differences in blood groups when they examined troops in the Macedonian army in Serbia during the last war. Many nationalities were represented, and they found that while all types tested had both A and B, yet there was a great preponderance of A in European and of B in Asiatic and African races. From these facts they drew the inference that the human race originally possessed neither A nor B, but that B arose on the central Asian plateau as a mutation in prehistoric times, while A appeared in northern Europe. The present mixtures would then be due to subsequent migrations and the intermingling of races. It has since become clear that the assumption of a single mutation, made by serologists, is not enough. In the absence of selection in its favor, a blood group gene will only increase and spread in the population if it occurs repeatedly, no matter how low the mutation frequency.

Probably over a million tests of human blood groups have since been made in all parts of the world, and the horizon regarding the history of the human blood groups has been greatly extended. A is found to be high not only in Europe but in many primitive races.[11] The latest full (although incomplete) list of published results is given by Boyd (1939). Routil, in 1932, found that 410,752 individuals had been tested throughout the world, giving totals of 37 per cent O,

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[11] In recent tests, 107 Guarani Indians in South Brazil and 237 Indians from N. E. Brazil were all O, indicating that O is probably widespread in South as in North America.

38 per cent A, 18 per cent B and 7 per cent AB. He also regarded O as the original condition in man, from which A and B had been derived, AB being the recombination occasionally arising in crosses of the other two. He pointed out that whereas O ranges from 1/5–4/5 (and 100 per cent) in different races, A is usually between 1/10 and 3/5 while B may vary from 0–1/2. A few of the characteristic results for different races are given in Tables 24 to 26.

Many racial indices have been formulated, especially to show the relative frequency of the genes for A and B, but their usefulness has been limited. Several methods of mapping and of plotting the results in co-ordinates or in a triangle have also been adopted.

TABLE 24

BLOOD GROUPS AND TYPES OF VARIOUS RACES

Author	*People*	*No.*	*O*	*A*	*B*	*AB*	*No.*	*M*	*MN*	*N*	*P*
Ikin, Prior, Race & Taylor (1939)	English	3696	43.7	44.2*	8.9	3.2					
Taylor & Prior (1938)	English	422	47.9	42.4†	8.3	1.4		28.7	47.4	23.9	
Landsteiner & Levine (1929)	New York, whites	265	41.5	46.8	9.8	1.9	532	26.1	53.5	20.3	50.6
Landsteiner & Levine (1929)	New York, Negroes	267	46.4	34.1	17.2	2.2	181	27.6	47.5	24.8	86.9
Fabricius-Hansen (1939)	Eskimos, E. Greenland	569	23.9	56.2	11.2	8.7		83.5	15.6	0.88	—
Sewall (1939)	Eskimos, Labrador & Baffinland	202	53.	46.	0	1.		31.7	50.5	17.8	—
Landsteiner, Wiener & Matson (1942)	Washington State Indians	120	73.3	25.8‡	0.8	0	120	56.7	39.2	4.2	
Levine, Matson & Schrader (1935)	Blackfoot & Blood Indians	176	20.5	78.4	0	1.1					
Matson & Schrader (1933)	Blackfoot	115	23.5	76.5	0	0					
	Blood Indians	24	16.7	83.3	0	0					
Matson, Levine & Schrader (1936)	Blackfoot (Montana)	103	24.3	74.8§	0	1.	93	54.7	40.	5.3	
Gates & Darby (1934)	British Columbia Indians	300	86.7	12.7	0.6	—					

* The 1537 A's were 22.1 per cent A_2. † The 156 A's were 18 per cent A_2.

‡ The 31 A's were all A_1.

§ The 93 A's (partly tested in a previous study) were 92 A_1, 1 A_2.

TABLE 24 (*continued*)

Author	*People*	*No.*	*O*	*A*	*B*	*AB*	*No.*	*M*	*MN*	*N*
Allen & Larsen (1937)	Pueblo Indians	140	78.6	20.7	0.7	0		59.3	32.9	7.8
Henckel, Castelli & Dal Borgo (1941)	Mapuche Indians	100						57.	34.	9.
See Wellisch (1935)	Ainu (Hidaka)	509	17.1	31.8	32.4	18.7				
See Wellisch (1935)	Ainu (Tokachi)	227	25.5	30.4	38.8	5.3				
See Wellisch (1935)	Ainu (Kamikawa)	200	36.	19.5	38.5	6.0				
See Wellisch (1935)	Ainu (Karafuto-Saghalien)	205	37.1	24.4	32.7	5.8				
Furuhata & Kishi	Ainu (Karafuto-Saghalien)	141	25.7	28.	34.8	11.5				
Kubo (1936)	Ainu						504	17.9	50.2	31.9
Haschimoto & Ischizu (1935)	Japanese						2001	27.8	53.8	18.3
Levine & Wong	Chinese, New York	150	30.	34.	25.3	10.7		23.3	54.7	22.0
Alley & Boyd (1943)	Chinese from Canton	101	45.5	29.7	18.8	5.9		38.6	45.5	15.8
Lo & Yang	Chinese Szechwan	1000	44.8	28.9	23.7	2.6				
Yang, Beh & Morse (1938)	Chwan Miao, Szechwan	205	36.1	11.2	39.	13.7				
Terada (1935)	Chinese in Formosa						1120	33.7	50.9	15.4
Terada (1935)	Taiyal, Formosa						812	22.3	69.3	8.4
Sai (1936)	Piawan, Formosa						716	5.7	84.1	10.2
Cleland & Johnston (1941)	Australian aborigines	1176	52.6	36.9	8.5	2.0				
Cleland & Johnston (1941)	South & Central Australian aborigines	842	38.7	61.3						
Birdsell	Australian aborigines						102	2.9	43.2	53.9
Birdsell & Boyd (1940)	Australian aborigines	805	53.2	44.7*	2.1	0	730	3.0	29.6	67.4
Gay (1942)	Australian aborigines (N.W.)	201	61.	39.						
Nigg (1930)	Hawaiians	413	36.5	60.8	2.2	0.5				
Nigg (1930)	Samoans	38	38.8	28.9	26.3	5.2				
Birdsell & Boyd (1940)	Tasmanian-Austr. hybrids	80	51.2	47.5	1.3	0	80	13.8	48.7	37.5
Wiener, Sonn & Yi (1944c)	Chinese	138	31.2	32.6†	27.5	8.7	138	31.9	46.4	21.7

* The 237 A were all A_1.

† These were all A_1.

TABLE 25

BLOOD GROUPS OF VARIOUS RACES

Author	*People*	*No.*	*O*	*A*	*B*	*AB*
See Wellisch (1935)	Usbeks	153	36.6	24.8	32.0	6.6
See Wellisch (1935)	Kirghis	914	36.8	23.9	31.4	7.9
See Wellisch (1935)	Albanians in Sicily	500	37.8	43.0	13.2	6.0
See Wellisch (1935)	Italians in Sicily		43.1	34.9	17.1	4.9
See Wellisch (1935)	Druses, Syria	229	33.2	36.3	18.3	12.2
Ganeff (1934)	Bulgarians	6,060	32.1	44.4	15.4	8.1
Boyd & Boyd (1937)	Basques, San Sebastian	91	57.2	41.7*	1.1	0
Irizar (1937)	Basques, San Sebastian	138	56.5	38.4	1.5	3.6
Mustakallio (1937)	Lapps, Finland	150	34.7	49.3	13.3	2.7
Mustakallio (1937)	Lapps, Sweden	404	28.9	62.6	4.5	4.0
Fisher & Taylor (1940)	Scotland	10,969	52.	34.2	10.4	3.3
Fisher & Taylor (1940)	N. England	8,716	48.6	40.3	8.5	2.5
Fisher & Taylor (1940)	S. England	106,477	45.2	43.2	8.5	3.1
Winkel (1936)	Abyssinians	400	42.7	26.5	25.3	5.5
Pijper (1935)	Hottentots	506	34.8	30.6	29.2	5.3
Pijper (1935)	Bushmen	548	57.1	29.5	6.8	6.6
Gusinde (1936)	Bushmen	——	56.1	29.6	7.5	6.8
Julien (1934)	Pygmies	1013	27.1	35.9	28.1	8.9
Gusinde (1936)	Pygmies, Efé (Bambuti)	1032	30.6	30.3	29.1	10.
Gusinde (1936)	Pygmies, Aka (Bambuti)	100	27.	41.	25.	7.
Pandit (1934)	Toda (India)	200	29.5	19.5	38.0	13.0
Aiyappan (1936)	Paniyan (India)	250	20.	62.4	7.6	10.
Majumdar (1942)	Tharus (India)	241	27.1	17.	37.5	18.4
Boyd & Boyd (1938)	Syrian Bedouin	304	39.8	23.4	30.2	6.6
Phillips (1931)	Maori, Te Arawa	127	38.6	41.7	0.8	18.9
Phillips (1931)	Maori, other tribes	73	63.0	35.6	1.4	0
Shapiro (1940)	Tahiti	124	35.5	58.9	4.8	0.8
Shapiro (1940)	Tuamotos (5 islands)	176	48.3	51.7	0	0
Shapiro (1940)	Australs	33	67.7	30.3	0	0
Shapiro (1940)	Rapa	6	33.3	66.6	0	0
Shapiro (1940)	Mangareva	29	41.4	58.6	0	0
Shapiro (1940)	Easter Island	21	33.3	66.6	0	0
Golden (1930)	Caraja (Brazil)	61	39.	5.	51.	5.
Rahm (1931)	Yaghan (Tierra del Fuego)	33	9.	0	91.	0
Rahm (1931)	Ona (Tierra del Fuego)	18	94.4	5.6		

* $A_2/A_1 = 0.39$.

TABLE 26

THE MN BLOOD TYPES OF VARIOUS RACES

People	*No.*	*M*	*MN*	*N*	*Author*
Irish, Dublin	399	30.	46.6	23.3	Boyd & Boyd (1937)
Egyptians	1145	27.	53.	20.	Boyd & Boyd (1937)
Egyptians	506	34.1	46.1	19.8	Matta (1937)
Danes	1485	30.	48.9	21.2	Wellisch (1935)
Danes, Copenhagen	580	30.	44.6	25.5	Thomsen & Clausen (1931)
Germans, Hamburg	4867	29.7	50.9	19.3	Lauer (1933)
Finns	400	23.	59.5	17.5	Wellisch (1935)
Congo pygmies	92	29.3	44.5	26.1	Jadin (1934)
Calcutta (Indians)	——	42.7	46.7	10.7	Greval (Macfarlane, 1940)
Syrian Bedouin	304	56.3	36.4	7.3	Boyd & Boyd (1938)
Basques	91	23.1	51.6	25.3	Boyd & Boyd (1937)

Some years ago (Gates, 1936) I developed a theory to account for the present racial distribution of the blood groups, based on the conceptions of parallel mutations and varying mutation frequencies. The conception of parallel mutations (Gates, 1912) was founded on the occurrence of similar (*lata*) mutations in different species of Oenothera, and Stomps (1912) independently found the *gigas* mutation in two different species. Later (Gates, 1920), the conception was further developed in relation to Oenothera, Drosophila and many wild species of plants. Vavilov (1922) showed extensive series of parallel or homologous variations (presumed mutations) in both wild and cultivated plants. The development of A and B independently in anthropoids and man is therefore not a priori improbable.

Very little is known as yet regarding mutation frequencies in wild species of plants and animals under natural conditions, although it is known that the same mutation often occurs repeatedly. There is also plenty of evidence that wild females of Drosophila and various plant species are heterozygous for different mutations. The subject of mutation rates was discussed (Gates, 1936) and the possibility that they may change from time to time was pointed out. In man, there is little evidence on the subject, but Haldane (1935) estimated the frequency of the hemophilia mutation at 1 in 50,000 in the population of London. Although all races produce albinos with a low frequency, the high proportion of albinos among the white Indians of Darien (see p. 285) can be most readily accounted for through a high mutation rate, and it is doubtful whether it can be explained in any other way except through the chance isolation of a family one of whom was heterozygous for this recessive condition. Streng (1937) also believes that blood group mutations occur, but so seldom that centuries must elapse before they affect the frequencies in a population.

That entirely new mutations begin to appear from time to time in various species is a necessary assumption to account for evolutionary diversity, and the principle of parallel mutations shows that the same mutation may occur independently in different species or groups. There is at present little evidence on which to build a theory of changes in mutation frequency, but to account for evolution it appears necessary to assume that at a particular point in the history of a species it began to produce certain mutations which had not appeared before. There is also evidence that particular species, for example, of Drosophila, produce different mutations (i.e., have different mutation frequencies) in different parts of their area of distribution. That being so, it is at least possible that the A and B blood group mutation rate may vary in different human races or may have so varied in the past. Such a theory appears necessary to account for the present known distribution of the B blood group.

The possibility was formerly considered (Gates and Darby, 1934), that the A and B both developed independently as parallel mutations in anthropoids and in man, since the anthropoid apes, as we shall see later, have among them both A and B. It soon transpired, however, that in many primitive or isolated peoples B was absent or in very low frequency, while A and O ranged between 40 per cent and 60 per cent. For such reasons, it was argued (Gates, 1929; Howells, 1933) that A is older in mankind than B. In northern Australia the aborigines appear to have derived their low percentage of B from Melanesians of adjacent New Guinea, while in central and southern Australia B disappears altogether. Recent results of Birdsell and Boyd (1940) show (Table 24) that the Australians are remarkably high in N. They suggest that three ethnic elements entered Australia between the late Pleistocene and early Recent times, the long intervals between allowing each to permeate the continent. From a few mixed descendants of Australian-Tasmanian crosses they conclude that the Tasmanians probably had no B, while their MN also was not very different from that of the Australians.

Similarly, Hawaiians (Nigg, 1930) have 60 per cent of A and only 2 to 3 per cent of B. The Maoris (Phillips, 1931) of New Zealand, who came from Hawaii about six hundred years ago, have the same blood groups (Table 25), except the Te Arawa tribe. The latter made its home in the Roturua district, into which the previous inhabitants of New Zealand, the Maoriri, retreated. The Maoriri differed from the Maori in having a fairer skin and a reddish tint in their hair. Four of the Te Awara tested showed these characters, and their very high percentage of AB seems to show clearly that the Maoriri had a high frequency of B. They, like the primitive Ainu (see below), must have achieved in some way a high concentration of B.

Shapiro (1940) finds that B is negligible or absent (Table 25) in central and eastern Polynesia, only slightly represented in Tahiti. But Samoa (Table 24), on the western margin of Polynesia, has 13 to 26 per cent B. The Samoans belong to the Tangaloa Polynesians (Handy, 1928) which got their B and some physical characters from South China. The Polynesians were evidently lacking in B when they left southeastern Asia.

The Paniyans (Aiyappan, 1936), a pre-Dravidian Australoid tribe in southern India, had 62 per cent A and 17.6 per cent B and AB, the

B probably derived from crossing with surrounding peoples high in B. The Bushmen of South Africa have nearly 60 per cent O, with about 30 per cent A and 10 to 13 per cent B.

The Basques are generally regarded as descended from the aborigines of southwestern Europe. More specifically (Coon, 1939) they are of Mediterranean Keltic Iron Age type with a mixture of Nordic and Dinaric elements (French Basques have 22 per cent blue eyes, 16 per cent light brown to blond hair, mesocephalic, C. I. 77, nose convex in 43–49 per cent). They number about 500,000 in northern Spain and 120,000 in the western French Pyrenees, they have rarely intermarried with other people (Wellisch, 1935), and their remarkable language is quite unrelated to the Indo-European tongues. They are of short stature, with a long triangular face, broad at the temples, with pointed chin, long thin nose and dark hair and they show wonderful suppleness and agility (see Ripley, 1923). The blood groups (Boyd and Boyd, 1937) show nearly 60 per cent O, 40 per cent A and only 1 to 2 per cent of B, in contrast to the values for B in the populations of Spain and France. Their peculiar facial type appears to be derived from a Mediterranean stock by isolation and inbreeding.

The Lapps number only about 20,000 stretching across the Arctic region of Europe — Norway, Sweden, Finland and Russia. They are also relatively low in B. Wellisch (1935) thinks they originated in inner Asia, which would account for their picking up some B in their migration northwestward to their present home. Table 27 shows the blood group relations of these peoples, together with Wellisch's useful "blood-chemical" formula.

TABLE 27

BLOOD-CHEMICAL FORMULAE OF CERTAIN PEOPLES

	O	*A*	*B*	*AB*	*Blood Chemical Formula*
Inner Asiatics	32.3	21.5	37.4	8.8	$A_4B_6O_{13}$
Ugro-Finns	32.9	28.7	31.2	7.2	$A_5B_5O_{13}$
Great Russians	32.0	37.7	22.9	7.4	$A_6B_4O_{13}$
Finns	32.8	42.9	17.8	6.5	$A_7B_3O_{13}$
Lapps	31.7	52.4	11.2	4.7	$A_8B_2O_{13}$

It will be seen that O is practically constant in these five peoples, while A shows a steady increase and B a corresponding decrease from top to bottom of the table.

These peripheral peoples, the Australians, Hawaiians, Maoris, Bushmen, Basques and Lapps, are all low in B or originally devoid of B. The Australian aborigines and the Bushmen are probably the most primitive surviving races, and the natural conclusion is that primitive (Paleolithic) man did not have B but did have A. These modern A-races now have about 40 per cent A, but it does not follow that they received this amount from their anthropoid ancestors. There may have been a considerable increase through the action of a low mutation rate in the long interval between man's origin and modern times.[12]

As pointed out elsewhere (Gates and Darby, 1934), if A accumulated in any race simply as the result of the mutation rate, the time necessary to attain say 40 per cent A from an original 100 per cent O can be calculated by the method of Fisher. If we assume that μ gametes mutate in each generation, then $1 - \mu$ remain normal, and after n generations $(1 - \mu)^n$ will remain normal. Let $(1 - \mu)^n = q$. Then $p = 1 - q$ is the proportion of mutated gametes. With random mating, the proportion of the three zygotic types will be in the well-known ratio q^2 normal : $2pq$ heterozygotes : p^2 homozygous mutants. Since μ is very small, q will only differ appreciably from unity when n is large. The expression $(1 - \mu)^n$ may then be replaced by $e^{-n\mu}$, so that $q = e^{-n\mu}$ or $n\mu = \log_e q$.

Applying this formula, if we assume a mutation frequency of 1 in a million, then in 10,000 generations with $\mu = 10^{-6}$, $n = 10^4$, p will be *ca.* 1 per cent. Or if $\mu = 10^{-5}$ and $n = 10^4$ (250,000 years, counting 25 years to a generation), then $p = 10$ per cent. In other words, with a mutation frequency of 1 in 100,000 it would require some 250,000 years to accumulate 10 per cent of the A blood group through mutation. Thus for the Australoids, the Polynesians, the Bushmen or the Basques to reach 40 per cent of A through mutation from O would require a million years. This is obviously too long a period, and so it seems more reasonable (Gates, 1939b) to assume that primitive man already had A, derived from his anthropoid ancestors. This is all the more likely since, (*a*) the blood groups show such stability that they can be used in tests of paternity, and (*b*) as we shall see below, the gorilla, chimpanzee, gibbon and orang utan, all have A, while the chimpanzee at least apparently has no B. While humanity thus began with a certain percentage of A, it was not necessarily 40 per cent. The remarkably uniform frequency of A in primitive and isolated races was not necessarily all acquired from our anthropoid ancestors, but may have been slowly increased through a persistent low mutation rate. A rate as low as 1 in 100,000 would be very difficult to detect in modern man.

On this basis A will have been derived, at least in large part, from man's anthropoid ancestors, while B may have arisen independently in the evolution of man, the gorilla, and the Asiatic orang and gibbon. In this connection it is significant that whereas the American Indians, Hawaiians and Australians tested for $\mathbf{A}_1$ and $\mathbf{A}_2$ were practically all of the $\mathbf{A}_1$ subgroup (Table 24), in Europeans about 20 per cent of the A's are $\mathbf{A}_2$. It therefore seems clear that $\mathbf{A}_2$ is a secondary mutation derived from the older $\mathbf{A}_1$. When the frequency of $\mathbf{A}_2$ is known in a wider range of races it may be possible to calculate roughly its mutation rate in different populations. Quite possibly the subgenes $\mathbf{A_2}$, $\mathbf{A_3}$, $\mathbf{B_2}$, $\mathbf{N_2}$ have a mutation rate which is high enough to be measured (i.e., they are relatively labile like the subgenes of color-blindness) while the main genes, **A** and perhaps **B**, are so stable that they very rarely mutate. We already have one record of $\mathbf{A_2}$ mutating to $\mathbf{A_1}$ (p. 699), while in the vastly greater number of tests for A there is only one case in which **A** has apparently mutated to **O**.[13] Haselhorst and Lauer (1931, 1932) found an **O** child from an $\mathbf{A_2B}$ mother, but it is a question whether its anaemic condition made difficulties for blood group determination. It was also a deaf-mute, nearly blind, and one side of its face was deformed. They are inclined to think that the child inherited A, but that its expression is inhibited, i.e., that there was a lack of penetrance. If such a child produced offspring the matter might be settled. Kossovitch (1929) reported another exception.

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[12] Simmons (1944) points out that A_2 is absent from Australians, Papuans, Fijians and Indonesians tested. All of the first three races and all but two of the Indonesians were Rh+. The Fijians were high and the Australians very high in N.

In this connection the Blackfoot and Blood Indians of Montana and Alberta, with their remarkably high concentration of 60 to 80 per cent A (Table 24) (whereas many Indian tribes appear to have been originally 100 per cent O), nevertheless agree with the Pueblos and the Mapuche of South America in having only 5 to 9 per cent of N. The Blackfoot may then have derived their high A through chance isolation of a family group with A from an ancestral tribe with only a very low percentage of A. But the matter is by no means settled. As regards the O, it may be that as the Indians gradually spread over the American continents, the A with which some of them entered America may have been left behind in the process of new colonization. A comparison of all the tribes will throw light on that possibility, but it would necessitate the assumption that the tribes reaching the British Columbia coast had already shed their A. It can generally be assumed (Gates and Darby, 1934) that a low percentage of A has been derived through crossing with whites. This certainly appears to be the case with the Nootka, Kwakiutl, Salish, Tshimshian and Haida of the British Columbia coast. The blood groups in relation to American Indian origins have been considered elsewhere (Gates and Darby, 1934). Anthropologists have not generally realized the importance of this evidence as a limiting factor. For instance, the British Columbia Indians, having no B, cannot have arrived in America very late. Wiener, Zepeda, *et al.* (1945) have recently tested 98 Mexican Indians, mostly full-blooded, from Tuxpan. Among other results, they found 90.8 per cent O, 6.1 per cent A_1, 3.1 per cent B. N was only 3.1 per cent, 21.1 per cent lacked P and 44.2 per cent lacked Hr. Besides the six allelic Rh genes they confirm Race *et al.* (1944) in finding one or two other genes which are rare in whites but had a frequency of 3.3 per cent in these Indians.

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[13] It seems clear that A, perhaps B, and Rh, contain labile sub-genes, and the same is true for the allelic forms of color-blindness. The extensive studies of Ernst (1942) on the highly labile gene for calycanthemy in Primulas, its various alleles and their mutations confirm this point of view.

The pedigree of an Indian family in British Columbia (Gates and Darby, 1934) shows the inheritance of **A** in four generations. Those who had died could of course not be tested, and III. 1 (living) was not tested. The family showed 8 A's (5 ♂ 3 ♀) in four generations, and four others who had died were probably A, as they were most likely to have transmitted it. This family accounted for 8 of the 14 who tested A in Klemtu village, the whole family giving 8 A and 8 O, and the whole village 14 A, 26 O, and 1 B who was negroid.

Considering now the distribution of B, there is much evidence that in humanity it is later in origin than A, but this evidence is not entirely unequivocal. Haldane (1940) calculates that the 10 to 15 per cent of B in European populations could not have been acquired through mutation in the 20,000 years (1000 generations) since the last retreat of the ice. It seems clear that most of the B in Europe is an infiltration from Asia within historical times, but this does not preclude a low mutation rate of B as well. From carefully sifted data of European populations, Haldane confirms the well-known gradient of B from East to West, but whereas in Table 26, for northern and eastern Europe, O remains relatively constant, he finds that O diminishes and B increases as we move eastward, A remaining relatively constant. This implies an older European population having roughly 40 per cent of A in equilibrium, with B as an intrusion from the east. On the other hand, the peripheral populations of western Europe show wide local variations in B because of early groups which contained B colonizing by sea. Farther north the O's stabilized at *ca.* 32 per cent. It seems likely that some B also came into southern Europe from across the Mediterranean within historical times. Bijlmer (1940) concludes that the B blood group has not come to the Netherlands with pigmentation from the south nor with brachycephaly from the east, but that pigmentation and B probably both came into Zealand by sea.

Candela (1942) has recently analyzed further the distribution of the B blood group in Europe. From a comparison of historical data (the Asiatic invasions of Europe beginning in the fifth and ending in the fifteenth century A.D.) with ethnic distributions and the present frequencies of the B blood group, he shows good reasons for the conclusion that the dolichocephalic Huns and the brachycephalic Avars in the fifth and sixth centuries, the Magyars in the ninth century and the Mongoloids under Genghis Khan in the thirteenth century were responsible for introducing the B blood group (as well as much brachycephaly) into European populations. He shows that the Russian and Danubian peoples who were mainly in the contact zone, from the Russian steppes to the Hungarian plains, have higher values of B (*q*), while the refugee ethnic groups of the Caucasus, such as the Ossetes and the Imeritini, remain almost as low in B as the Basques of western Europe. The Mongoloid aspect in the contact zone is largely dissipated because it is determined by many independently assorting genes, while the B blood group is a single indivisible unit handed down to succeeding generations.

The Hirszfelds were certainly right in regarding Asia as the main centre of origin of B. It runs up to high values in Central Asia, India, Mongolia and Japan. It is rather a surprise that the primitive and long isolated Ainu (Table 24) are very high in B, and this applies equally to the purer Ainu in Saghalien and Kamikawa (in North Hokkaido). In blood groups they are most like the Usbeks and Kirghis (Table 25) of central Asia, but this does not necessarily indicate relationship. The northern Ainu, in Saghalien and Kamikawa, have more O and less A than the southern Ainu, who are more mixed with the Japanese. That this mixing has not raised the frequency of B, shows that they were already at least as high in B as the Japanese. They also differ from the Japanese in having about 10 per cent less M and 10 per cent more N, agreeing in this with the Australian aborigines.

Some anthropologists have regarded the Ainu as a remnant of a "white" race originally occupying the eastern Asiatic islands from Sumatra to the Philippines, represented by the Batak of Sumatra, the Dyaks of Borneo, the Tayals of Luzon and the Bizaja of Mindanao. Others relate them more nearly with Caucasians, but their high B is difficult to account for on this basis. They seem definitely to be Asiatics, although their white skin, dolichoid skull and somewhat wavy hair may relate them to the Caucasian stock. The skin color varies from white to olive, yellow, red-brown, light copper red, brown, dark brown, and nearly black according to early authors. The dark skin is due to black hairs, according to some, but the babies are quite white.

The problem of the Ainu is discussed in a series of papers in the Proc. 3rd Pan-Pacific Science Congress (1928). Their language appears to be related to the Malayan, Melanesian and Nicobar tongues, although Aryan affinities have been suggested. Siberian place-names such as Tomsk, Irkutsk, Omsk, and Obi are said to be Ainu, but the -sk ending is Russian. Sternberg regards them as Australoid in affinities, as shown in part by their hairy bodies and luxuriant beards, as well as their dolichocephaly and broad noses. Comparison with the Indian Todas seems less justified. There are no remains of the Ainu in Corea, but there are Neolithic Ainu remains in the Luchu (Ryukyu) Islands south of Japan, and many of the people in these islands are said to have Ainu features. This appears to be good evidence that the Ainu entered Japan from the south, but leaves their high percentage of B unaccounted for. If they left southeast Asia with an early stock of Australoids and moved northward, through the islands of the western Pacific, they might have picked up some B in the screen of islands extending from Borneo to Formosa. They may then be regarded as wanderers from the same original source as the Australoids of Australia, south India, and West Oceania. Their connections with Siberia will have come later, when they moved northward from Japan. From Siberian sources, they have picked up such culture elements as the bear ceremonies, but their contacts have scarcely been sufficient to account for the B blood group being as high as in Japanese and Mongolians.

The Chwan Miao of western China are another aboriginal people with as much as 39 per cent B and very low A.

Other unexplained pockets of high B are the Eskimos of East Greenland (Table 24) as determined by Fabricius-Hansen (1939), in contrast to those of Labrador and Baffinland, who have practically no B. This is also difficult to account for without invoking B mutations. The 708 Eskimos at Angmassalik in East Greenland were all of pure stock except three Eur-Eskimo children. At Thule they were 80 per cent O. The Eskimos are believed to have arrived in North Greenland over Smith Sound prior to A.D. 982. On the southeast coast they met the Northmen immigrants in the twelfth century and the latter were exterminated in the fifteenth century, after being cut off from Europe. It is assumed that the Eskimos migrated up the east coast of Greenland in the fourteenth century. Even if they had already mixed with the Northmen, this would not account for their high per cent of B. For the origin of the Eskimo, see Jenness (1933).

In South America, the Caraja in Brazil and the Yaghan of Tierra del Fuego (Table 25) show remarkably high concentrations of B.

Africa appears to be an independent centre of the B mutation, although the frequency is not so high as in Asia. In South Africa B generally runs in the 20's (Elsdon-Dew, 1936) but the Hottentots have nearly 30 per cent and the Bushmen only 6 to 8 per cent (Table 25). The African distributions require special study, as the blood-grouping results give rather a different picture from the current anthropological views. Elsdon-Dew concluded that the Bantu are the most primitive black race, having been isolated in Africa before A and B appeared. We have, on the contrary, regarded the presence of some A as primitive, the 100 per cent O of many American Indian tribes being a result of repeated migrations and isolations in new areas. The African pygmies are high in B, and crossing with Negroes reduces its frequency.

It seems possible to conclude that in various parts of the world the B blood group has come in later than the A and has probably increased through mutation in particular areas. It thus appears to resemble genetically the brachycephalic type of skull, which has arisen in various parts of the world, apparently from the older dolichocephalic type of head (see Chap. XXX). The A blood group, on the other hand, and the capacity for producing the A mutation, have probably been inherited from our anthropoid ancestors. Areas of high concentration, such as the Blackfoot Indians and related tribes, may result partly from a higher mutation rate or entirely from chance isolates of population.

The Tharus are a tribe in North India, between Nepal and the United Provinces. Majumdar (1942) finds (see Table 25, p. 713) that they are very high in B, which may have been derived from mixture with Mongoloids. They are notoriously immune to malaria, and 78 per cent of those with the B or AB blood group said they were free from malaria, while those with "fever" were mostly A. It seems that the Tharus children get the disease and develop an enlarged spleen, but by the age of twelve or fifteen they have developed immunity. From this it appears that the presence of B may offer a selective advantage in malarial districts. This factor might account for the high B in some tribes occupying malarial regions, but there are many cases (e.g., Tierra del Fuego and East Greenland) which could not be accounted for in this way.

It is sometimes supposed that in mixed races blood group determinations can yield no evidence regarding the racial history, but this is far from true. Ottensooser (1944) has developed a formula by which the degree of mixture of races may be calculated. If r_1 is the percentage of a gene in the larger population, r_m in the mixed population and r_2 in the smaller population, then the degree of mixture is $X = \frac{r_m - r_2}{r_1 - r_2}$.

The large numbers of blood groups determined in connection with the blood transfusion service in Britain during the war have now made possible an analysis of the blood group frequencies in different parts of the island. O and A show wide variations in frequency. For southern England alone over 106,477 results have already been compiled. Fisher and Taylor (1940) show a consistent gradient in the frequency of A from southern England to Scotland. The higher O in Scotland presumably indicates peripheral isolation, the blood groups being closely similar to those of Iceland. Both are lower in A and B than modern Norway, indicating that the early Viking population of Norway has since been infiltrated with ethnic elements from further south. Hart (1944) shows that in North Ireland the English element (surnames) differs from the Scotch and Irish, these two latter being the same: North Wales is much higher than England in B, and Iceland is very similar to Dublin.

Other comparative results for O and A in different parts of Britain show that B and AB together make up 12 to 15 per cent while O and A fluctuate reciprocally. Ireland has decidedly more O than Britain, indicating greater isolation. In North Wales, Fraser Roberts found that when only donors with Welsh surnames were taken, A was as low as in the Scots and Irish, while English family names gave a proportion of A almost as high as in southern England. Among families with Welsh surnames, those which are characteristic of North Wales are lower in A than those which are commoner in South Wales. Surnames were not adopted in Wales until Tudor times. Similarly in the Bristol area, those with Highland Scottish and Irish surnames were higher in O and lower in A. In South Wales, which speaks a different form of Welsh from North Wales, the blood groups were essentially like the south of England. It is thus clear that, with large numbers, very considerable ethnic diversity can be shown by the blood groups within the British Isles. Fisher and Roberts (1943) have recently found in parts of England a slight but significant excess of men who are A and of women who are O.

Similarly in Syria, Wellisch (1935) finds the following formulae applicable:

Druses	$A_9B_5O_{19}$
Mohammedans	$A_8B_5O_{19}$
Jews	$A_9B_6O_{18}$
Christians	$A_9B_3O_{19}$

The distribution of the blood groups among the many racial types of India offers special problems which we need not enter into here. From the work of Macfarlane (1938, 1941), Sarkar and others it may be pointed out that the highest frequency of B, and perhaps the original source of B in India, is among the lower castes in the northeast (Bengal). Both A and B are lower (and O higher) in the Brahmins and other high castes. The various jungle tribes (aborigines) vary widely, but most of them, such as the Santal, Oraon, Bhil, Korku and Kanikkar, are higher in B than A. The Bhils vary, however, in different areas, and Majumdar (1942) found only 26 per cent of B in the Bhils of Gujarat. There is a general increase in A and B from south to north, and in B from east to west across Central India.

The results suggest that there were originally pre-Dravidian Australoid stocks in southern India high in A but with little or no B, and others such as the Oraon somewhat farther north high in B and low in A. The O blood group reaches about 50 per cent in the Oraon and Kanikkars. The Oraon of India are comparable with the Chwan Miao of western China as centres for B, but there is no present reason for connecting the two. Since the Australians were originally without B and since there are good grounds for believing that they migrated from southeastern Asia, leaving behind such A-peoples as the Paniyans of southern India (and the Veddas of Ceylon), this is another reason for assuming that the B is later in origin or at least in expansion than A. The Polynesians, who probably left southeastern Asia much later than the Australoids, were also without B. Everything therefore points to a relatively late expansion of B, and it is difficult to see how this could have been accomplished in the absence of a relatively high mutation rate. The scattered pockets of B in the Eskimos, on the Amazon and in Tierra del Fuego all appear to be of recent origin however this has taken place.

TABLE 28

RESULTS OF BLOOD GROUPING MUMMIES AND BONES

	No.	*O*	*A*	*B*	*AB*	*?*	
Egyptian mummies Predynastic		3	—	1	2	—	Boyd & Boyd, 1937
Egyptian mummies *18th* dynasty		2	—	6	3	—	Candela, 1936
Egyptian mummies Total		93	3	12	9	5	Boyd & Boyd, 1937
Pueblo Indian mummies		22	—	—	—	2	Boyd & Boyd, 1937
Basket Maker Indian mummies		27	3	1	0		Boyd & Boyd, 1937
Peruvian Indian mummies		118	1	6	2	7	Boyd & Boyd, 1937
Minnesota*	6	1	5	—	—		Candela, 1937
New York City†	4	—	—	4			Candela, 1937
Aleutian mummies	30	36.6	36.6	20	6.6		Candela, 1939

* As these bones were associated with a tooth of an extinct bison, they are presumably Indian and are regarded as not less than three hundred years old.

† These were believed to be from an early colonial burial. One was identified as a Negro, from the hair and other characters.

Recent work in the blood grouping of mummies and human bones (using absorption methods) has a bearing on these problems if the results are sufficiently reliable for acceptance. That successful methods may be developed is indicated by the fact that when Dr. Boyd sent Dr. Candela ten specimens of human bones which had been artificially aged by different methods, from individuals whose blood groups were known, he (Candela, 1940) successfully determined the correct blood group in nine of them. Some of the results are given in Table 28. These results would indicate that while the modern Pueblo Indians have about 20 per cent A and probably no B except from an occasional cross, the prehistoric Pueblos were in the same condition although no A was actually found. The early Peruvian Indians on this basis would have more B than A and the Aleutian mummies from pre-Russian times 20 per cent of B. Unfortunately, the blood groups of the modern Aleuts have not been taken.

Blood Groups of Anthropoids

Obviously the blood groups of anthropoids are important in relation to the origin of the human blood groups. The results, as they stand at present, are given in Table 29. Over 80 per cent of the chimpanzees tested are A, the rest O, B apparently absent. In tests made of gorillas from the urine, Candela (1940) formerly concluded that two were AB, but later tests of the blood showed that these were actually both B. An interesting and probably significant difference appears between the lowland gorilla (*G. gorilla*) and the mountain species, *G. beringei*,

TABLE 29

BLOOD GROUPS OF ANTHROPOIDS

	No.	*O*	*A*	*B*	*AB*	*Doubtful*	*Remarks*
Chimpanzee	99	12	85			2	Candela, Wiener & Goss, 1940
Gorilla gorilla			—	5		—	Candela, Wiener & Goss, 1940
Gorilla gorilla				3			Wiener, Candela & Goss, 1942
Gorilla gorilla	—	—	—	5		—	Wiener, Candela & Goss, 1942
G. beringei			2				
Orang utan	22	—	8	10	4		Candela, 1940
Gibbon	15	—	2	7	2	4	Candela, 1940
M. mulatta	4	—	—	4			belonging to one family
M. mulatta	5	—	—	5			Wiener, Candela & Goss, 1942
M. irus (Java)	8	1	7				in family I
M. irus (Java)	4		—	1	3		in family II
Ateles ater	6		6	—	—		Wiener, Candela & Goss, 1942
A. cucullatus	5	1	—	4	—		Wiener, Candela & Goss, 1942

the former having only B and the latter only A in the few tested. The Asiatic anthropoids, on the other hand, both have A, B and AB in similar proportions, but apparently lack O. The B of the gorilla is found (Candela, Wiener and Goss, 1940) to be similar to but not identical with the human B, as the red cells were only feebly agglutinated by human anti-B sera. An extract of the gorilla's submaxillary gland gave results closely parallel to those of a human B individual. Landsteiner and Miller (1925) showed the presence of B-like agglutinogens in the red cells of New World monkeys and lemurs, but their absence from the Old World monkeys. This argues for the independent development of B in New World monkeys, lemurs and the higher anthropoids.

Wiener, Candela and Goss (1942) have recently tested three more lowland gorillas. The human agglutinogens A and B were absent from the red cells but the serum of the gorilla Janet contained only anti-A. The submaxillary gland contained group-substances similar to or identical with the human B. Landsteiner's rule regarding the reciprocal relationship of antigens and agglutinins thus holds true as far as the organs (but not the red cells) are concerned. The saliva and urine of two young gorillas also contained B.

In seventeen macaques the saliva, glands and urine agreed in placing each in one group. Although the red cells in all were negative, the reciprocal agglutinins were present in the serum. Other unpublished results give a total of thirteen lowland gorillas tested, all B.

Various tests on monkeys showed that in the Simiidae and Hylobatidae, as in man, when A is present in the red cells the β agglutinin is in the serum, and similarly for the other blood groups. In the Cercopithecidae, however, the red cells do not contain the agglutinogens A or B, but the sera nevertheless contain the α and β agglutinins. In the rhesus monkey (*M. mulatta*), α but not β is regularly present and the tissues, urine and saliva (but not the red cells) show the presence of B; while in Cercopithecus β is apparently present, but not α. Other workers have shown that in baboons and other monkeys one agglutinin or the other may be present, depending on the individual. As seen in Table 29, four rhesus monkeys were all B in saliva, urine and tissues, and many previous experiments indicate that B is universal in the rhesus monkey. The twelve Java macaques were distributed in A, B or AB, as would be expected from inheritance in the two families. The reciprocal relation of agglutinogen and agglutinin found in man and the great apes is thus shown to apply to the monkeys generally but not to their red cells. Since the chimpanzee is the only anthropoid in which O has yet been found, Candela, Wiener and Goss

(1940) suggest that possibly all individuals were originally AB, and O is a loss mutation. The apparent absence of B from this species makes this view difficult to accept, although it may ultimately prove to be correct. Dahr (1940) tested anthropoid sera against anthropoid and human corpuscles and thus showed the presence of β in A-anthropoids, α in B-anthropoids, both α and β in O-chimpanzees, while in AB-orangs α and β were absent. As heteroagglutinins against the corpuscles of the great apes are generally also present in human sera, the latter are not suitable for testing the A and B in anthropoids.

Tests by Wiener *et al.* (1942) of six black spider monkeys (*Ateles ater*) showed the presence of A in the saliva, although the red cells were negative. Similarly, five gray spider monkeys (*Ateles cucullatus*) were tested; four showed B in the saliva and α in the serum, while one tested O in the saliva and $\alpha\beta$ in the serum, the red cells being negative in all. Thus there is a tendency in many species of primates for one blood group to be predominantly or exclusively present. Further exploration may, however, change this picture, and in any case it appears most probable that the origin of one group from another through mutation has occurred independently in different species. That these have been loss mutations, ending with O, is not impossible on general grounds.

The results with primates indicate, as Wiener (1943) points out, that the A and B group substances were present in the organs and secretions of lower primates, only appearing in the red cells at a higher stage of evolution. Wiener, Boyd and others believe that the present distribution of A, B and O in man and anthropoids can be accounted for by crossing between races which were originally pure for one group. This simply throws the origin of the blood group differences one step further back. Instead of a differentiation of races through low mutation rates extending over long periods, we would have the rare occurrence of single mutations. But in the absence of selection, the mere isolation of a group in which such a mutation had occurred would not produce a race with a high frequency of the A or B. Of course, migration and crossing will account for many features of agglutinogen distribution, such as the B in Europe, but this does not touch the fundamental question of the origin of the racial differences. In this respect the serological view does not meet all the known genetical facts.

Landsteiner and Wiener (1937) tested the blood of several Old World and New World monkeys for M. They found both M and N in ten chimpanzees and M always present in the rhesus monkey, and concluded that the M agglutinogen is limited to Primates. Wiener (1938) confirmed that M and N are present in all chimpanzees, but not identical with human M and N. He showed the presence of M in gibbons, orangs and certain lower monkeys and recently in the gorilla Janet with less similarity to the human according to their position in the evolutionary scale. Different rabbits are found to produce qualitatively different M-agglutinins. Dahr (1939) confirms that lemurs and New World monkeys do not have the M, N which are present in the Old World monkeys. He finds the B of the orang indistinguishable from human B, while B-like substances are widely present in the lower mammals such as the mouse, rat, rabbit, guinea pig, cat, pig, donkey and cattle. He also finds serological incompatibility between the Platyrrhine (New World) and Catarrhine (Old World) monkeys, as shown by reciprocal agglutination of their red cells.

Only brief reference can be made to the numerous serological studies in other animals. In rabbits (Keeler and Castle, 1934), two agglutinogens, $\mathbf{H}_1$ and $\mathbf{H}_2$, are found, as well as **O**. $\mathbf{H}_1$ and $\mathbf{H}_2$ are both dominant to **O**. The corresponding agglutinins are secondarily produced. Thus an **O** mother injected with $\mathbf{H}_1\mathbf{H}_2$ blood develops both $\mathbf{h}_1$ and $\mathbf{h}_2$ agglutinins in her blood and these are transmitted through her placenta to her offspring, but there is no harmful effect. The agglutinogens were found to be already developed in the nucleated blood cells (normoblasts) of a 4-mm. embryo. Knopfmacher (1942) has found a third isohaemagglutinogen, $\mathbf{H}_6$, independent of the alleles $\mathbf{H}_1$ and $\mathbf{H}_2$. He also found that the homozygous and heterozygous conditions could be distinguished by the strength of the clumping. Sawin and colleagues (1943, 1944), in further studies, find that some rabbits have the α agglutinin for human A cells, some that for B and some that for O. The gene **An** produces antigen in the serum, but no α agglutinin. It is dominant to **an** which produces antibodies but not antigen in the serum. The **A** antigen in rabbits is linked to the gene for brachydactyly.

In fowls, the work of Todd (1930) and Thomsen (1936) has shown the presence of a large but not unlimited number of inherited antigens. Stormont and Cumley (1943) have shown the presence of thirty different inherited antigens in the red cells of cattle. These are, however, hemolysins, requiring the presence of "complement" from rabbit serum, and producing laking of the corpuscles. Each is represented by a gene. The number of chromosome pairs is also thirty, but there is evidence of linkage between some of these genes.

One more immunological study may be referred to because of its special genetic interest. Irwin and his colleagues have made extensive studies of the serological differences in certain dove hybrids, and their inheritance. In the latest papers (Cumley and Irwin, 1942), the inheritance of the various antigens in the pearlneck (*Streptopelia chinensis*) and the ring dove (*S. risoria*) and their hybrids has been analyzed to show their Mendelian inheritance. The pearlneck is found to have ten or more species-specific antigens, which distinguish its red cells from those of the ring dove. Each is determined by one or more genes, on separate chromosomes since they show genetic segregation in the hybrids. By immunizing a rabbit with red cells of the pearlneck, four kinds of specific antibodies are produced, only one of which is the same as one in the ring dove. The latter has another which is not found in the pearlneck. By back-crosses of the hybrids to the two parent species, these specific elements could be segregated and analyzed. In another cross (Irwin and Cumley, 1942) between the ring dove and the pigeon (*Columba livia*), it was similarly shown that these species have certain proteins in common and certain others which are specific for each species, again showing that genes determine the chemical constitution of the various proteins involved. In this sense the blood groups can be regarded as cell characters, fairly close developmentally to the genes that produce them, and perhaps indeed identical with them.

In the ring dove × pearlneck a "hybrid" substance appears. This is composed of three antigens, two of which show complete linkage with certain pearlneck characters.

By crosses between the Senegal dove and the ring dove, Cumley, Irwin and Cole (1943) show that antigens in the serum are controlled by genes which segregate independently from antigens in the red corpuscles. A further study by Cumley and Irwin (1944) of the blood cell antigens in various species, shows that the species fall into two separate groups — Old World and New World. There are many gene-determined antigens in each species and an early evolutionary separation of the two groups is indicated. It is thus clear that in birds the antigens and their inheritance can furnish evidence of phylogeny.

In crosses between mallard and Muscovy ducks, McGibbon (1944) found six specific antigens (two of them in the same chromosome), showing evidence of segregation. Some were possessed by each species and others were common to both. The F_1 sterile hybrids all had also a "hybrid" substance presumably derived from the interaction of genes.

These and various other results indicate that many biochemical syntheses are controlled by single genes in the cell. E. B. Wilson originally suggested that the chromosomes produce or contain enzymes. It seems that not only are large numbers of antigens in animals and man direct gene products, but that the same is true of many enzymes. Indeed it appears that these genes can be directly identified with the corresponding enzyme or antigen (see Sturtevant, 1944, and Emerson, 1944).

LITERATURE

Aiyappan, A. 1936. Blood-groups of the pre-Dravidians of the Wynaad Plateau, India. *Man* 36:191–194.

Allen, F. W. & Larsen, H. D. 1937. Heredity of agglutinogens M and N among Pueblo and Blackfoot Indians. *J. Immunol.* 32:301–305.

Alley, O. E. & Boyd, W. C. 1943. The M, N types of Chinese from Canton. *Am. J. Phys. Anthrop.* N.S. 1:301–304.

Baar, H. S. 1945. The Race-Wiener test in haemolytic disease of the new-born. *Nature* 155:789–790.

Bauer, K. H. 1928. Zur Lösung des Problems der Blutgruppenvererbung. *Klin. Wochens.* 7:1588–1592.

Benians, T. H. C. & Feasby, W. R. 1941. Raynaud's syndrome with spontaneous cold haemagglutination. *Lancet* 241:479–480.

Bernstein, F. 1924. Ergebnisse einer biostatistischen zusammenfassenden Betrachtung über die erblichen Blutstrukturen des Menschen. *Klin. Wochens.* 3:1495–1497.

———. 1925. Zusammenfassende Betrachtungen über die erblichen Blutstrukturen des Menschen. *Zeits. Abst. u. Vererb.* 37:237–270.

———. 1930. Über die Erblichkeit der Blutgruppen. *Zeits. Abst. u. Vererb.* 54:400–426.

———. 1930. Fortgesetzte Untersuchungen aus der Theorie der Blutgruppen. *Zeits. Abst. u. Vererb.* 56:233–273.

———. 1931. Zur Grundlegung der Chromosomentheorie der Vererbung beim Menschen. *Zeits. Abst. u. Vererb.* 57:113–138.

Bijlmer, H. J. T. 1940. Contribution to the anthropology of the Netherlands. *Proc. Konink. Nederl. Akad. Wetens.* 43:113–139.

Birdsell, J. B. & Boyd, W. D. 1940. Blood groups of the Australian aborigines. *Am. J. Phys. Anthrop.* 27:69–90.

Boorman, K. E. & Dodd, B. E. 1943. The group-specific substances, A, B, M, N and Rh: their occurrence in tissues and body fluids. *J. Pathol. & Bact.* 55:329–339.

Boorman, K. E., Dodd, B. E. & Mollison, P. L. 1942. The clinical significance of the Rh factor. *Brit. Med. J.* ii. 535–538, 569–572.

——— ——— ———. 1945. Iso-immunization to the blood group factors A, B and Rh. *J. Path. & Bact.* 57:157–169.

Boyd, W. C. 1939. Blood groups of American Indians. *Am. J. Phys. Anthrop.* 25:215–235.

———. 1939a. Blood groups. *Tabulae Biol.* 17:113–240.

———. 1943. *Fundamentals of Immunology.* New York. Intersci. Publishers. Pp. 446.

———. 1945. Rh blood factors: an orientation review. *Arch. of Path.* 40:114–127.

Boyd, W. C. & Boyd, L. G. 1937. Blood grouping tests on 300 mummies. *J. Immunol.* 32:307–319.

——— ———. 1937. New data on blood groups and other inherited factors in Europe and Egypt. *Am. J. Phys. Anthrop.* 23:49–70.

Boyd, W. C. & Hooker, S. B. 1938. Note on the mechanism of specific agglutination. *Proc. Soc. Exp. Biol. Med.* 39:491–496.

Boyd, W. C. & Warshaver, E. R. 1945. Serological relationship of blood group A and B antigens; production of anti-B precipitins. *J. Immunol.* 50:101–106.

Boyden, A. A. 1934. Precipitins and phylogeny in animals. *Amer. Nat.* 68:516–536.

———. 1943. Serology and animal systematics. *Amer. Nat.* 77:234–255.

Brahn, B., Schiff, F. & Weinmann, F. 1932. Über die chemische Natur der Gruppensubstanz A. *Klin. Wochens.* ii. 1592.

Bruynoghe, G. 1936. L'excrétion des agglutinogènes. *Compt. Rend. Soc. de Biol.* 122:472–474.

Bühler, E. 1935. Untersuchungen über die Erblichkeit des Isoagglutinintiters. *Zeits. Abst. u. Vererb.* 70:463–467.

Candela, P. B. 1936. Blood-group reactions in ancient human skeletons. *Am. J. Phys. Anthrop.* 21:429–432.

———. 1937. Blood group determinations upon Minnesota and New York skeletal material. *Am. J. Phys. Anthrop.* 23:71–78.

———. 1939. Blood-group determinations upon the bones of thirty Aleutian mummies. *Am. J. Phys. Anthrop.* 24:361–383.

———. 1940. New data on the serology of the anthropoid apes. *Am. J. Phys. Anthrop.* 27:209–221, 479–480.

———. 1940. Reliability of blood-group tests on human bones. *Am. J. Phys. Anthrop.* 27:365–381.

———. 1942. The introduction of blood-group B into Europe. *Human Biol.* 14:413–443.

Candela, P. B., Wiener, A. S. & Goss, L. J. 1940. New observations on the blood group factors in Simiidae and Cercopithecidae. *Zoologica* 25:513–521.

Chester, K. S. 1937. A critique of plant serology. *Quart. Rev. Biol.* 12:19–46, 165–190, 294–321.

Cleland, J. B. & Johnston, T. H. 1941. Blood grouping of Australian aborigines at Ooldea, South Australia. *J. Trop. Med.* 44:76–78.

Cooley, T. B. 1941. Hereditary factors in the blood dyscrasias. *Am. J. Dis. Child.* 62:1–8.

Coombs, R. R. A. & Race, R. R. 1945. Further observations on the "incomplete" or "blocking" Rh antibody. *Nature* 156:233.

Cumley, R. W. & Irwin, M. R. 1942. Genetic segregation of antigens. III. *J. Hered.* 33:357–365. Figs. 6.

——— ———. 1944. The correlation between antigenic composition and geographic range in the Old or New World of some species of Columba. *Amer. Nat.* 78:238–256.

——— ———. 1942. Immunogenetic studies of species: segregation of serum components in backcross individuals. *Genetics* 27:177–192.

Cumley, R. W., Irwin, M. R. & Cole, L. J. 1943. Genic control of species-specific antigens in serum. *J. Immunol.* 47:35–51.

Dahr, P. 1938. Untersuchungen über die Möglichkeit einer serologischen Unterscheidung homozygoter und heterozygoter A und B-Menschen. *Zeits. f. Imm-forsch.* 92:180–220.

Dahr, P. 1939. Zur Frage der serologischen Verschiedenheit von niederen Altweltaffen (Catarrhini) und Neuweltaffen (Platyrrhini). *Zeits. f. Rassenphysiol.* 11:30–41.

———. 1940. Über Blutgruppen bei Anthropoiden. *Zeits. f. Morph. u. Anthr.* 38:38–45.

———. 1941. Serologische Untersuchungen bei 330 Zwillingspaaren. *Zeits. f. Rassenphysiol.* 12:1–17.

Dahr, P. & Bussmann, W. 1938. Familienuntersuchungen über die Vererbung der "Untergruppen" A_1 und A_2. *Zeits. f. Rassenphysiol.* 10:49–64.

Dahr, P., Offe, H. & Weber, H. 1940. Weitere Erblichkeitsuntersuchungen über den Blutfaktor P bei Familien und Zwillingen. *Zeits. f. Rassenphysiol.* 11:78–93.

Darrow, R. R. 1938. Icterus gravis (erythroblastosis) neonatorum. *Arch. of Pathol.* 25:378–417.

Decastello, A. & Sturli, A. 1902. *Münch. Med. Wochens.* 49:1090–1095.

Della Vida, B. L. & Dyke, S. C. 1941. Absorption of isoagglutinins from pooled plasma or serum. *Lancet* 240:564–565.

Diamond, L. K., Blackfan, K. D. & Baty, J. M. 1932. Erythroblastosis fetalis and its association with universal edema of the fetus, icterus gravis neonatorum and anemia of the newborn. *J. Pediat.* (St. Louis) 1:269–309.

Dockeray, G. C. & Sachs, H. 1944. Rh antibodies in the maternal circulation without clinical manifestations of erythroblastosis in the child. *J. Immunol.* 48:241–246.

von Dungern, E. & Hirszfeld, L. 1910. Über Vererbung gruppenspezifischer Strukturen des Blutes. *Zeits. f. Immun. exp. Therapie* 6:284–292.

Elsdon-Dew, R. 1936. *Publ. S. Afr. Inst. Med. Res.* 7:217.

Emerson, S. 1944. The induction of mutations by antibodies. *Proc. Nat. Acad. Sci.* 30:179–183.

Epstein, A. A. & Ottenberg, R. 1908. A simple method for performing serum reactions. *Trans. N. Y. Pathol. Soc.* 8:117–123.

Ernst, A. 1942. *Vererbung durch labile Gene.* Zürich.

Fabricius-Hansen, V. 1939. Blood groups and MN types of Eskimos in East Greenland. *J. Immunol.* 36:523–530.

Ferguson, L. C., Stormont, C. & Irwin, M. R. 1942. On additional antigens in the erythrocytes of cattle. *J. Immunol.* 44:147–164.

Fisher, R. A. & Roberts, J. A. F. 1943. A sex difference in blood-group frequencies. *Nature* 151:640–641.

Fisher, R. A. & Taylor, G. L. 1940. Scandinavian influence in Scottish ethnology. *Nature* 145:590.

Fisher, R. A. & Vaughan, Janet. 1939. Surnames and blood groups. *Nature* 144:1047–1048.

Friedenreich, V. 1935. Ein erblicher defekter N-Receptor, der wahrscheinlich eine bisher unbekannte Blutgruppeneigenschaft innerhalb des MN-Systems darstellt. *Deut. Zeits. ges. Gericht. Med.* 25:358–368.

———. 1936. Eine bisher unbekannte Blutgruppeneigenschaft (A_3). *Zeits. f. Immunitäts.* 89:409–422.

———. 1938. Blood groups and genetics. *Ann. of Eugen.* 8:152–165.

Friedmann, L. & Tschkonja, E. 1932. Blutgruppen und der Durchmesser der Blutkörperchen. *Folia Haem.* 48:261–265.

Furuhata, T. 1927. On the heredity of the blood groups. *Jap. Med. World* 7: No. 7. Pp. 13.

———. 1928. On the heredity of the blood groups. *Verh. V. Internat. Kongr. Vererb.* i:705–735. Pls. 3.

*Gammelgaard, A. & Marcussen, P. V. 1940. *Zeits. f. Immunitäts.* 98:411.

Gates, R. R. 1912. Parallel mutations in *Oenothera biennis*. *Nature*, 89:659–660.

———. 1921. *Mutations and Evolution.* Cambridge Press; also in *New Phytol.* Vol. 19. 1920.

———. 1929. Blood groups of Canadian Indians and Eskimos. *Am. J. Phys. Anthrop.* 12:475–485.

———. 1936. Recent progress in blood group investigations. *Genetica* 18:47–65.

———. 1938. The blood groups and other features of the Micmac Indians. *J. Roy. Anthrop. Inst.* 68:283–298. Pls. 3.

———. 1939a. Blood groupings and racial classification. *Am. J. Phys. Anthrop.* 24:385–390.

———. 1939b. Rise and spread of the A and B blood groups from the mutationist point of view. *Zeits. f. Rassenk.* 11:58–63.

Gates, R. R. & Darby, G. E. 1934. Blood groups and physiognomy of British Columbia coastal Indians. *J. Roy. Anthrop. Inst.* 64:23–44. Pls. 5.

Gay, R. K. 1942. Blood grouping of aborigines of north-west Australia. *Med. J. Australia* 2:435–436.

Golden, G. 1930. Distribution of blood groups in South American Indians. *Lancet* 219:278–279.

Graves, W. W. 1934. A note on the possible relation of blood groups to age and longevity. *Ann. Int. Med.* 8:747–751.

———. 1935. Note sur une relation éventuell entre les groups sanguines, l'age et la longevité. *L'Anthropologie* 45:601–608.

Haldane, J. B. S. 1935. The rate of spontaneous mutation of a human gene. *J. Genet.* 31:317–326.

———. 1940. The blood-group frequencies of European peoples, and racial origins. *Human Biol.* 12:457–480.

———. 1942. Selection against heterozygotes in man. *Ann. Eugen.* 11:333–340.

Handy, E. S. 1928. Probable sources of Polynesian culture. *Proc. 3rd Pan-Pac. Congr.* 2:2459–2468.

Hart, E. W. 1944. An analysis of the blood-group composition of a population in Northern Ireland. *Ann. Eugen.* 12:89–101.

Haselhorst, G. & Lauer, A. 1931. Über eine Blutgruppenkombination Mutter AB und Kind O. *Zeits. f. Konst-lehre* 15:205–222. Figs. 2.

——— ———. 1932. Zur Blutgruppenkombination Mutter AB und Kind O. *Zeits. f. Konst-lehre* 16:227–230.

Hawksley, J. C. & Lightwood, R. 1934. A contribution to the study of erythroblastosis: icterus gravis neonatorum. *Quart. J. Med.* 27:155–209. Pls. 5.

Heidelberger, M. 1938. Protein constitution and immunological behavior *Cold Spring Harbor Symposia on Quant. Biol.* 6:369–375.

Heidelberger, M. & Kendal, F. E. 1935. Precipitin reaction between type III pneumococcus polysaccharide and homologous antibody. III. A quantitative study and a theory of the reaction mechanism. *J. Exp. Med.* 61:563–591.

Henckel, K. O., Castelli, A. & Dal Borgo, J. 1941. *Bol. Soc. Biol. Concepcion* 15:37–41.

Hirszfeld, L. 1928. *Konstitutionsserologie und Blutgruppenforschung.* Berlin. Pp. 235.

Hirszfeld, L. & H. 1919. Serological differences between the blood of different races. *Lancet* ii. 675–679.

Hirszfeld, L. & Kostuch, Z. 1938. Über das Wesen der Blutgruppe O. *Klin. Wochens.* 17:1047–1051.

Hollingsworth, M. W. 1928. Blood transfusion by Richard Lower in 1665. *Ann. Med. History* 10:213–225. Figs. 3.

Howells, W. W. 1933. Anthropometry and blood types in Fiji and the Solomon Islands. *Anthrop. Papers, Amer. Mus. Nat. Hist.* 33:283–339.

Hunt, A. B. 1945. The Rh factor in repeated abortion and miscarriage. *Proc. Mayo Clinic* 20:26–28.

Hyman, H. S. 1935. Genetic studies of the agglutinogens M and N. *J. Immunol.* 29:223–237.

———. 1937. The development of the agglutinogens M and N in newborn infants. *Abst. of Doctors Diss.* Ohio State Univ. No. 21. Pp. 187–193.

Hyman-Parker, H. S. 1942. The development of the agglutinogens M and N in newborn infants. *J. Immunol.* 43:1–11.

Ikin, E. W., Prior, A. M., Race, R. R. & Taylor, G. L. 1939. The distributions in the A_1A_2BO blood groups in England. *Ann. Eugen.* 9:409-411.

Irwin, M. R. & Cumley, R. W. 1942. Immunogenetic studies of species: qualitative differences in the serum of back-cross progeny following a generic cross in birds. *Genetics* 27:228–237.

*Jansky, J. 1907. Haematologische Studien bei Psychotikern. *Kliniky Sbornik* No. 2.

Jenness, D. (Editor). 1933. *The American Aborigines.* Toronto Univ. Press. Pp. 396.

Kass, E. H. 1945. The occurrence of normal serum gamma-globulin in human lymphocytes. *Science* 101:337–338.

Keeler, C. E. & Castle, W. E. 1934. Blood group inheritance in rabbits. *J. Hered.* 25:433–439. Figs. 8.

Khanolkar, V. R. & Sanghvi, L. D. 1945. Distribution of the Rh factor in Indians. *Nature* 155:427.

Kidder, G. W., Stuart, C. A., McGann, V. G. & Dewey, V. C. 1945. Antigenic relationships in the genus Tetrahymena. *Physiol. Zool.* 18:415–425.

Knopfmacher, H. P. 1942. A study of four antigenic components of rabbits' erythrocytes. *J. Immunol.* 44:121–128.

Koller, Theo. 1927. Untersuchungen über das Verhältnis der Blutgruppen bei Müttern und ihren Neugeborenen, mit spezieller Berücksichtigung der gegenseitigen Isoagglutination. *Arch. J. Klaus-Stift.* 2:247–272.

Koller, T. & Meier, U. M. 1928. Isoagglutinine im Serum der Neugeborenen. *Arch. J. Klaus-Stift.* 3:219–238.

Kosjakov, P. N. & Tribulev, G. P. 1939. The effect of temperature and drying upon the M- and N-factors of the human blood. *J. Immunol.* 37:297–304.

Kossovitch, N. 1929. Les groupes sanguins chez les Français et les règles de l'hérédité. *Rev. Anthropol.* 39:374–379.

Kubo, T. 1936. On the agglutinogens M and N of the Ainu. *J. Immunol.* 30:287–290.

Landsteiner, K. 1900. Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe. *Zentlbl. f. Bakt., Parasit. u. Infekt.* 27:357–362.

———. 1945. *The Specificity of Serological Reactions.* Harvard Press. Pp. 310.

Landsteiner, K. & Harte, R. A. 1940. On group specific A substances. IV. The substance from hog stomach. *J. Exp. Med.* 71:551–562.

Landsteiner, K. & Levine, P. 1928a. On individual differences in human blood. *J. Exp. Med.* 47:757–775.

——— ———. 1928b. On the inheritance of agglutinogens of human blood demonstrable by immune agglutinins. *J. Exp. Med.* 48:731–749.

——— ———. 1929. On the racial distribution of some agglutinable structures of human blood. *J. Immunol.* 16:123–131.

——— ———. 1931. The differentiation of a type of human blood by means of normal animal serum. *J. Immunol.* 20:179–185.

Landsteiner, K. & Miller, C. P., Jr. 1925. Distribution of serological factors related to human isoagglutinogens in the blood of lower monkeys. *J. Exp. Med.* 42:863–872.

Landsteiner, K., Strutton, W. R. & Chase, M. W. 1934. An agglutination reaction observed with some human bloods, chiefly among negroes. *J. Immunol.* 27:469–472.

Landsteiner, K. & Wiener, A. S. 1937. On the presence of M agglutinogens in the blood of monkeys. *J. Immunol.* 33:19–25.

——— ———. 1940. An agglutinable factor in human blood recognized by immune sera for rhesus blood. *Proc. Soc. Exp. Biol. & Med.* 43:223–224.

——— ———. 1941. Studies on an agglutinogen (Rh) in human blood reacting with anti-rhesus sera and with human antibodies. *J. Exp. Med.* 74:309–320.

Landsteiner, Wiener & Matson. 1942. Distribution of the Rh factor in American Indians. *J. Exp. Med.* 76:73–78.

Landsteiner, K. & Witt, D. H. 1926. Observations on the human blood groups. *J. Immunol.* 11:221–247.

Langley, F. A. & Stratton, F. 1944. Haemolytic disease in the newborn: the Rh factor. *Lancet* 246:145–148.

Lattes, L. 1932. *The Individuality of the Blood.* London.

Learmonth, J. R. 1920. The inheritance of specific isoagglutinins in human blood. *J. Genet.* 10:141–148.

Levine, P. 1942. Genetic and constitutional causes of fetal death. *Collecting Net* 17:88–89.

———. 1942. On human anti-Rh sera and their importance in racial studies. *Science* 96:452–453.

———. 1944. Mechanism of the isoimmunization by the Rh factor of red blood cells. *Arch. of Path.* 37:83–90.

———. 1945a. Prevention of unintentional isoimmunization of the Rh negative female population. *J. Am. Med. Assn.* 128:946.

———. 1945b. Anti-Hr sera. *Nature* 156:418–419.

Levine, P., Burnham, L., Katzin, E. M. & Vogel, P. 1941. The role of iso-immunization in the pathogenesis of erythroblastosis fetalis. *Am. J. Obstet. & Gynec.* 42:925–937.

Levine, P. & Gilmore, E. L. 1945. The first stage of antigen-antibody reaction in infectious mononucleosis. *Science* 101:411–412.

Levine, P., Katzin, E. M. & Burnham, L. 1940. Atypical warm isoagglutinins. *Proc. Soc. Exp. Biol. Med.* 45:346–348.

——— ——— ———. 1941. Isoimmunization in pregnancy, its possible bearing on the etiology of erythroblastosis foetalis. *J. Am. Med. Assn.* 116:825–827.

Levine, P. & Katzin, E. M. 1941. Pathogenesis of erythroblastosis fetalis: absence of the Rh factor from saliva. *Proc. Soc. Exp. Biol. Med.* 48:126–129.

Levine, P., Matson, G. A. & Schrader, H. F. 1935. Distribution of blood groups and agglutinogen M among Indian "Blackfeet" and "Blood" tribes. *Proc. Soc. Exp. Biol. Med.* 33:297–299.

Levine, P. & Stetson, R. 1939. An unusual case of intra-group agglutination. *J. Am. Med. Assn.* 113:126.

Levine, P., Vogel, P., Katzin, E. M. & Burnham, L. 1941. Pathogenesis of erythroblastosis fetalis: statistical evidence. *Science* 94:371–372.

Levine, P. & Wong, H. 1943. The incidence of the Rh factor and erythroblastosis fetalis in Chinese. *Am. J. Obstet. & Gynec.* 45:832–835.

Lubinski, H., Benjamin, B. & Strean, G. 1945. The distribution of the Rh factor in Jewish mothers and infants and the incidence of haemolytic anaemia in Jewish newborn infants. *Canad. Med. Assn. J.* 53:28–30.

McCall, A. J. 1945. Haemolytic disease with incomplete Rhesus antibody. *Brit. Med. J.* i. 343–344.

McCall, A. J. & Holdsworth, S. 1945. Haemolytic disease of the new-born caused by the antibody St. *Nature* 155:788–789.

Macfarlane, Eileen W. E. 1938. Blood-group distribution in India with special reference to Bengal. *J. Genet.* 36:225–237.

———. 1940. Mother and child combinations of blood groups and blood types and their development in Bengalis. *J. Roy. Asiatic Soc. Bengal* 5:71–86.

———. 1941. Blood groups among Balahis (weavers), Bhils, Korkus and Mundas, with a note on Pardhis, and aboriginal blood types. *J. Roy Asiatic Soc. Bengal* 7:15–24. Pl. 1.

Macfarlane, Eileen W. E. 1941. Tibetan and Bhotia blood group distributions. *J. Roy. Asiatic Soc. Bengal* 7:1–5.

Macfarlane, E. W. E. & Sarkar, S. S. 1941. Blood groups in India. *Am. J. Phys. Anthrop.* 28:397–410.

McFeeters, J. W. 1939. Morbid inheritance in an isolated rural community. *Brit. Med. J.* i. 218–220.

McGibbon, W. H. 1944. Cellular antigens in species and species hybrids in ducks. *Genetics* 29:407–419.

Macklin, M. T. 1937. Erythroblastosis fetalis: a study of its mode of inheritance. *Am. J. Dis. Child.* 53:1245.

———. 1944. The diagnosis of Rh incompatibility, especially by microscopic appearances. *J. of Pediat.* 25:533–554. Figs. 14.

Majumdar, D. N. 1942. Blood groups of the Bhils of Gujarat. *Current Sci.* 11:353–354.

———. 1942. Tharus and their blood groups. *J. Roy. Asiatic Soc. Bengal* 8:25–37. Pls. 2.

Malone, E. 1945. Foetal erythroblastosis and hydrops in twins. *Brit. Med. J.* ii. 496.

Marrack, J. R. 1938. The chemistry of antigens and antibodies. *Med. Res. Council, Special Rept. Series.* No. 230. Pp. 194. London.

Matson, G. A. & Schrader, H. F. 1933. Blood grouping among the "Blackfeet" and "Blood" tribes of American Indians. *J. Immunol.* 25:155–163.

——— ———. 1941. The distribution of the four blood groups among the Ute Indians of Utah. *Proc. Utah Acad. Sci. Arts & Lett.* 18:101–103.

Matson, G. A., Levine, P. & Schrader, H. F. 1936. Distribution of the sub-groups of A and the M and N agglutinogens among the Blackfeet Indians. *Proc. Soc. Exp. Biol. & Med.* 35:46–47.

Matta, D. 1937. A critical investigation of the blood groups and their medico-legal application. *Fac. Med. Cairo.* Publ. No. 11.

Morgan, W. T. J. 1943. An artificial antigen with blood-group A specificity. *Brit. J. Exp. Pathol.* 24:41–49.

Morgan, W. T. J. & Van Heyningen, R. 1944. The occurrence of A, B and O blood group substances in pseudo-mucinous ovarian cyst fluids. *Brit. J. Exp. Pathol.* 25:5–15.

Morgan, W. T. J. & Watkins, W. M. 1944. A blood-group A antigen prepared from an A-hapten of human origin. *Brit. J. Exp. Pathol.* 25:221–228.

Moss, W. L. 1910. Studies on isoagglutinins and isohemolysins. *Bull. J. Hopkins Hosp.* 21:63–70.

Mourant, A. E. 1945. A new Rhesus antibody. *Nature* 155:542.

Murray, J. 1944. Rh antenatal testing. *Lancet* 247:594–596.

———. 1944a. A nomenclature for the subgroups of the Rh factor. *Nature* 154:701–702.

Murray, J., Race, R. R. & Taylor, G. L. 1945. Serological reactions caused by the rare human gene R_z. *Nature* 155:112–113.

Myslivec, V. 1944. A contribution to the study of human blood groups. *J. Roy. Anthrop. Inst.* 71:67–83. Figs. 13.

Myslivec, V. 1945. Contribution to the analysis of the exceptions to Bernstein's Theory. *Human Biol.* 17:13–45.

Nigg, Clara. 1930. A study of the blood group distribution among Polynesians. *J. Immunol.* 19:93–98.

Nuttall, G. H. F. 1904. *Blood Immunity and Blood Relationship.* Cambridge Press. Pp. 444.

Oliver-González, J. & Torregrosa, M. V. 1944. A substance in animal parasites related to the human isoagglutinogens. *J. Infect. Dis.* 74:173–177.

Ottenberg, R. 1923. Hereditary blood qualities: statistical considerations. *J. Immunol.* 8:11–17.

*Ottensooser, F. 1944. Cálculo do grau de mistura racial através dos grupos sangüíneos. *Rev. Brazil. Biol.* 4:531–537.

Owen, J. Lewis. 1928. Some observations on blood grouping. *Edin. Med. Journ.* 35:222–235.

Parish, H. J. & Macfarlane, R. G. 1941. Effect of calcium in a case of autohaemagglutination. *Lancet.* 241:477–479.

Pauwen, L. J. & Moureau, P. 1939. Critique de la nouvelle théorie héréditaire des groupes d'iso-agglutination de Dawood Matta. *Zeits. Vererb. u. Konstit.* 22:699–702.

Phillips, G. 1931. The blood groups of the Maori. *Human Biol.* 3:282–287.

Pietrusky, F. 1940. Zur Vererbung der Blutgruppeneigenschaft N_2. *Zeits. f. Immunitätsforsch.* 98:387–390.

Pijper, A. 1934. Blood group and red-cell diameter. *S. Africa Med. J.* Oct. 13.

Pinkerton, F. J. 1944. Rh blood types in Hawaii. *Hawaii Med. J.* 4:84–85.

Polayes, S. H. 1945. Erythroblastosis fetalis in mothers with Rh-positive blood. *Am. J. Dis. Child.* 69:99–102.

Race, R. R. 1944. An "incomplete" antibody in human serum. *Nature* 153:171–172.

———. 1944a. Some recent observations on the inheritance of blood groups. *Brit. Med. Bull.* 2:421.

Race, R. R., McFarlane, M. & Cappell, D. F. 1945. Anti-Hr serum of Levine. *Nature* 155:542–543.

Race, R. R., Taylor, G. L., Boorman, K. E. & Dodd, B. E. 1943. Recognition of the Rh genotypes in man. *Nature* 152:563–564.

Race, R. R., Taylor, G. L., Cappell, D. F. & McFarlane, M. N. 1944. Recognition of a further common Rh genotype in man. *Nature* 153:52–53.

Race, R. R., Taylor, G. L., Ikin, E. W. & Prior, A. W. 1944. The inheritance of allelomorphs of the Rh gene in fifty-six families. *Ann. Eugen.* 12:206–210.

Ripley, W. Z. 1923. *The Races of Europe.* New York. Pp. 624.

Roberts, J. A. F. 1942. Blood-group frequencies in North Wales. *Ann. of Eugen.* 11:269–271.

———. 1942. Surnames and blood groups, with a note on a probable remarkable difference between North and South Wales. *Nature* 149:138.

Rothen, A. 1945. Forces involved in the reaction between antigen and antibody molecules. *Science* 102:446–447.

Routil, R. 1932. Welche Bedeutung haben die menschlichen Blutgruppen für eine Rassendiagnose. *Biol. Generalis* 8:283–300.

Sachs, H. 1943. Exceptionally weak reactivity of a blood agglutinogen in two sisters (sub-group A_3). *J. Path. & Bact.* 55:109–111.

Sawin, P. B., Griffith, M. A. & Stuart, C. A. 1944. Genetic linkage of blood types in the rabbit. *Proc. Nat. Acad. Sci.* 30:217–221.

Sawin, P. B., Stuart, C. A. & Wheeler, K. M. 1943. Pictorial presentation of antigen and antibody relations. *J. Hered.* 34:179–186. Figs. 5.

Schäfer, K. & Gennerich, H. 1939. Die Blutgruppenspezificität der Thrombocyten. *Klin. Wochens.* 18:491–492.

Schiff, F. 1931. *Die Gruppensubstanzen des menschlichen Körpers.* Jena.

———. 1940. Racial differences in frequency of the "secreting factor." *Am. J. Phys. Anthrop.* 27:255–262.

Schiff, F. & Sasaki, H. 1932. Der Ausscheidungstyp, ein auf Serologischem Wege nachweisbares mendelndes Merkmal. *Klin. Wochens.* ii. 1426–1429.

Schwartz, H. A. & Levine, P. 1943. Studies on the Rh factor. *Am. J. Obst. & Gynec.* 46:827–835.

Sewall, K. W. 1939. Blood, taste, digital hair and color of eyes in Eastern Eskimo. *Am. J. Phys. Anthrop.* 25:93–99.

Shapiro, H. L. 1940. The distribution of blood groups in Polynesia. *Am. J. Phys. Anthrop.* 26:409–416.

Simmons, R. T. 1944. The Rh factor: ethnological aspects. *Med. J. Austral.* 31:483–485.

Simmons, R. T., Graydon, J. J. & Hamilton, R. 1944. The Rh factor in the blood of Australian aborigines. *Med. J. Austral.* 31:553–554.

Simmons, R. T., Graydon, J. J., Jakobowicz, R. & Bryce, L. M. 1943. The Rh factor. *Med. J. Austral.* ii. 496–501.

Simmons, R. T., Graydon, J. J. & Ouwehand, C. 1945. Blood groups, M, N types and the Rh factor in Indonesians. *Med. J. Austral.* 32: i. 108–110.

Smith, C. H. 1928. Isoagglutinins in the blood of the newborn, with special reference to their placental transmission. *Am. J. Dis. Child.* 36:54–69.

Snyder, L. H. 1925. Human blood groups and their bearing on racial relationships. *Proc. Nat. Acad. Sci.* 11:406–407.

———. 1926. Human blood groups: their inheritance and racial significance. *Am. J. Phys. Anthrop.* 9:233–263.

———. 1926. The linkage relations of the blood groups. *Zeits. f. Immun. u. exp. Therapie* 49:464–480.

———. 1929. *Blood Grouping in Relation to Clinical and Legal Medicine.* Baltimore. Pp. 153.

———. 1945. The nomenclature of the Rh blood types. *Science* 101:62.

Steffan, Paul. 1932. *Handbuch der Blutgruppenkunde.* Munich. Pp. 669.

Stern, C. & Charles, D. R. 1945. The Rhesus gene and the effect of consanguinity. *Science* 101:305–307.

Stevens, W. L. 1938. Estimation of blood-group gene frequencies. *Ann. Eugen.* 8:362–375.

Stomps, T. J. 1912. Die Entstehung von *Oenothera gigas* de Vries. *Ber. Deut. Bot. Gesells.* 30:406–416.

Stormont, C. & Cumley, R. W. 1943. Cellular antigens in cattle blood. *J. Hered.* 34:35–41. Figs. 5.

Strandskov, H. H. 1944. Physiological aspects of human genetics, five human blood characteristics. *Physiol. Revs.* 24:445–466.

Stratton, F. 1943. Some observations on autohaemägglutination. *Lancet* 244:613–614.

———. 1944. Rh antibodies in human sera; a new variety. *Nature* 153:773.

Streng, O. 1937. Blutgruppenforschung und Anthropologie. *Zeits. f. Rassenphysiol.* 9:97–111.

Sturtevant, A. H. 1944. Can specific mutations be induced by serological methods? *Proc. Nat. Acad. Sci.* 30:176–178.

Suk, V. 1933. Faultless teeth and blood groups. *Publ. Fac. Sci. Univ. Masaryk.* No. 125, figs. 8.

Sumner, J. B., Howells, S. F. & Zeissig, A. 1935. Canavallin A and haemagglutination. *Science* 82:65–66.

Taylor, G. L. & Prior, A. M. 1938. Blood groups in England. I. Examination of family and unrelated material. *Ann. Eugen.* 8:343–355.

——— ———. 1938. II. Distribution in the population. *Ann. Eugen.* 8:356–361.

——— ———. 1939a. III. Discussion of the family material. *Ann. Eugen.* 9:18–44.

——— ———. 1939b. The distribution of the M and N factors in random samples of different races. *Ann. Eugen.* 9:97–108.

Taylor, Race & Prior. 1942. Optimal proportions of antigen and antibody in tests for Rh antibodies. *Brit. Med. J.* ii. 572–574.

Thalhimer, W. & Myron, S. A. 1942. Globulin fractions of A and B agglutinating serums for blood typing. *J. Am. Med. Assn.* 118:370–372.

Thomsen, O. 1930. Die Erblichkeitsverhältnisse der menschlichen Blutgruppen mit besonderer Hinblick auf zwei "neue," A^1 und A^1B genannte Blutgruppen. *Hereditas* 13:121–163.

———. 1934. Über das Verhältnis zwischen Isolysin und Isoagglutinin. *Zeits. f. Rassenphysiol.* 7:1–16.

———. 1936. Untersuchungen über erbliche Blutgruppenantigene bei Hühnern II. *Hereditas* 22:128–144.

Thomsen, O. & Clausen, J. 1931. Das Vorkommen von Landsteiner's "Immunreceptoren" M und N in der Dänischen Bevölkerung. *Hereditas* 15:213–218.

Thomsen, O., Friedenreich, V. & Worsaae, E. 1930. Über die Möglichkeit der Existenz zweier neuer Blutgruppen. *Acta Path. Scand.* 7:157–190.

Todd, C. 1930. Cellular individuality in higher animals, with special reference to the individuality of the red blood corpuscles. *Proc. Roy. Soc.* 106B:20–44.

Vavilov, N. I. 1922. The law of homologous series in variation. *J. Genet.* 12:47–89. Pls. 2.

Vorsschulte, A. & Ziegler, K. 1935. Zum Frage Blutgruppe und Scharlach. *Deut. Med. Wochens.* 61:262–263.

Waller, R. K. & Levine, P. 1944. On the Rh and other blood factors in Japanese. *Science* 100:453–454.

Waller, R. K., Levine, P. & Garrow, I. 1944. A case of erythroblastosis caused by immunization of an Rh-positive mother by the Rh factor. *Am. J. Clin. Path.* 14:577–581.

Wellisch, S. 1935. Rassenreste und Volkssplitter. *Zeits. f. Rassenphysiol.* 7:99–110.

———. 1938. Das vorhandene Untersuchungsmaterial im MN-System. *Zeits. f. Rassenphysiol.* 10:65–68.

———. 1938. Fortschritte der Blutgruppenforschung. *Zeits. f. Rassenphysiol.* 10:27–35.

Wiener, A. S. 1938. The agglutinogens M and N in anthropoid apes. *J. Immunol.* 34:11–18.

———. 1941. Hemolytic reactions following transfusions of blood of the homologous group. II. *Arch. of Pathol.* 32:227–250.

———. 1942. The Rh factor and racial origins. *Science* 96:407–408.

———. 1943. *Blood Groups and Blood Transfusions.* 3rd Edn. C. C. Thomas. Pp. 438.

———. 1943. Evolution of the human blood group factors. *Amer. Nat.* 77:199–210.

———. 1943a. Distribution and heredity of variants of the Rh type. *Science* 98:182–184.

———. 1944. Nomenclature of the Rh blood types. *Science* 99:532–533.

———. 1944a. The Rh series of allelic genes. *Science* 100:595–597.

———. 1945. Theory and nomenclature of the Hr blood factors. *Science* 102:479–482.

Wiener, A. S., Belkin, R. B. & Sonn, E. B. 1944. Distribution of the A_1–A_2–B–O, M–N, and Rh blood factors among Negroes in New York City. *Am. J. Phys. Anthrop.* N.S. 2:187–194.

Wiener, A. S., Candela, P. B. & Goss, L. J. 1942. Blood-group factors in the blood, organs and secretions of Primates. *J. Immunol.* 45:229–235.

Wiener, A. S., Davidsohn, I. & Potter, E. L. 1945. Observations on the relation of factor Hr to the Rh blood types. *J. Exp. Med.* 81:63–72.

Wiener, A. S. & Forer, S. 1941. A human serum containing four distinct isoagglutinins. *Proc. Soc. Exp. Biol. Med.* 47:215–218.

Wiener, A. S. & Karowe, H. E. 1944. Diagrammatic representation of the human blood group reactions. *J. Immunol.* 49:51–61. Figs. 7.

Wiener, A. S. & Kosofsky, I. 1941. Quantitative studies on the group-specific substances in human blood and saliva. I. Group-specific substance B. *J. Immunol.* 41:413–428. II. Group-specific substance A with special reference to the subgroups. *J. Immunol.* 42:381–393.

Wiener, A. S. & Landsteiner, K. 1943. Heredity of variants of the Rh type. *Proc. Soc. Exp. Biol. Med.* 53:167–170.

Wiener, A. S. & Rothberg, S. 1933. Heredity of the subgroups of group A and group AB. *Human Biol.* 5:577–586.

Wiener, A. S. & Silverman, J. 1940. Permeability of the human placenta to antibodies. *J. Exp. Med.* 71:21–27.

Wiener, A. S. & Silverman, J. 1941. Subdivisions of group A and group AB with special reference to the so-called agglutinogen A_3. *Am. J. Clin. Path.* 11:45–53. Figs. 2.

Wiener, A. S. & Sonn, E. B. 1943. Heredity of the Rh factor. *Genetics* 28:157–161.

———— ————. 1945. Heredity of the Rh blood types. IV. Medicolegal application in case of disputed parentage. *J. Lab. Clin. Med.* 30:395–404.

Wiener, A. S., Sonn, E. B. & Belkin, R. B. 1944a. Heredity of the Rh blood types. *J. Exp. Med.* 79:235–253.

———— ———— ————. 1944b. The nature of Rh agglutination reactions. *Science* 100:98–99.

Wiener, A. S., Sonn, E. B. & Yi, C. L. 1944. Blood groups, subgro M-N and Rh types in Chinese. *Am. J. Phys. Anthrop.* N.S. 2:267–27

Wiener, A. S., Unger, L. J. & Sonn, E. B. 1945. New data on the distribution of the Rh blood types. *Proc. Soc. Exp. Biol. Med.* 58:89–92.

Wiener, A. S., Zepeda, J. P., Sonn, E. B. & Polivka, H. R. 1945. Individual blood differences in Mexican Indians, with special reference to the Rh blood types and the Hr factor. *J. Exp. Med.* 81:559–571.

Witebsky, E., Anderson, G. W. & Heide, A. 1942. Demonstration of Rh antibody in breast milk. *Proc. Soc. Exp. Biol. Med.* 49:179–183.

Witebsky, E. & Klendshoj, N. C. 1941a. Blood group specific substances and blood transfusions. *Science* 94:256–267.

————. 1941b. The isolation of an O specific substance from ga juice of secretors and carbohydrate-like substances from gastric juice of non-secretors. *J. Exp. Med.* 73:655–667.

Witebsky, E., Klendshoj, N. C. & Swanson, P. 1941. Preparation and transfusion of safe universal blood. *J. Am. Med. Assn.* 116:2654–2656.

Witebsky, E. & Mohn, J. F. 1945. Investigations on the occurrence of Rh substances in amniotic fluid. *J. Exp. Med.* 82:143–156.

Wolfe, H. R. 1939. Standardization of the precipitin technique and its application to studies of relationships in mammals, birds and reptiles. *Biol. Bull.* 76:108–120.

Yang, S. C. H., Beh, Y. T. & Morse, W. R. 1938. Blood groups of the aboriginal Ch'wan Miao of Szechwan Province, West China. *Man* 38:65–67. Pl. 1.

Young, L. E. 1945. The active and passive acquisition of α_1 agglutinins by A_2 patients as a result of blood transfusion. *J. Immunol.* 51:101–110.

Yudin, S. S. 1937. Transfusion of stored cadaver blood. *Lancet* 233:360–366.